Responses to the White House Office of Science and Technology Policy Request for Information on Clinical Research Infrastructure and Emergency Clinical Trials

Request for Information (RFI) on Clinical Research Infrastructure and Emergency Clinical Trials

Federal Register :: Request for Information; Clinical Research Infrastructure and Emergency Clinical Trials

SUMMARY:

In accordance with the 2022 National Biodefense Strategy for Countering Biological Threats, Enhancing Pandemic Preparedness, and Achieving Global Health Security (National Biodefense Strategy) and the American Pandemic Preparedness Plan (AP3), the White House Office of Science and Technology Policy (OSTP), in partnership with the National Security Council (NSC), is leading efforts to ensure that coordinated and large-scale clinical trials can be efficiently carried out across a range of institutions and sites to address outbreaks of disease and other emergencies. Efforts in this area could include the establishment of a U.S.-level governance structure and outreach to a wide range of institutions, clinical trial networks, and other potential trial sites that can participate in emergency research, both domestically and internationally. A further goal of this emergency clinical trials initiative is to support the expansion of clinical research into underserved communities, and increase diversity among both trial participants and clinical trial investigators. Building U.S. capacity to carry out emergency clinical trials will enlarge and strengthen the U.S. clinical trials infrastructure overall.

DATES:

Interested persons and organizations are invited to submit comments on or before 5 p.m. ET on December 27, 2022.

ADDRESSES:

Interested individuals and organizations should submit comments electronically to *emergencyclinicaltrials@ostp.eop.gov* and include "Emergency Clinical Trials RFI" in the subject line of the email. Due to time constraints, mailed paper submissions will not be accepted, and electronic submissions received after the deadline cannot be ensured to be incorporated or taken into consideration.

Instructions

Response to this RFI is voluntary. Each responding entity (individual or organization) is requested to submit only one response. Please feel free to respond to one or as many prompts as you choose.

Please be concise with your submissions, which must not exceed 8 pages in 12-point or larger font, with a page number on each page. Responses should include the name of the person(s) or organization(s) filing the comment.

OSTP invites input from all stakeholders, including members of the public, representing all backgrounds and perspectives. In particular, OSTP is interested in input from research institutions, clinical trialists, health care providers interested in clinical research, contract research organizations (CROs) and other clinical trial service providers, pharmaceutical and biotechnology companies, and community health care organizations. *Please indicate which of these stakeholder types, or what other description, best fits you as a respondent.* If a comment is submitted on behalf of an organization, the individual respondent's role in the organization may also be provided on a voluntary basis.

Comments containing references, studies, research, and other empirical data that are not widely published should include copies or electronic links of the referenced materials. No business proprietary information, copyrighted information, or personally identifiable information should be submitted in response to this RFI. Please be aware that comments submitted in response to this RFI may be posted on OSTP's website or otherwise released publicly.

In accordance with FAR 15.202(3), responses to this notice are not offers and cannot be accepted by the Federal Government to form a binding contract. Additionally, those submitting responses are solely responsible for all expenses associated with response preparation.

FOR FURTHER INFORMATION CONTACT:

For additional information, please direct questions to Grail Sipes at 202-456-4444 or *emergencyclinicaltrials@ostp.eop.gov*.

SUPPLEMENTARY INFORMATION:

Background: Currently, the U.S. clinical trials infrastructure is not well prepared to carry out coordinated, large-scale clinical research in the event of an outbreak of infectious disease or other public health emergency. As was seen in the initial stages of the COVID-19 outbreak, different institutions and networks tend to implement their own research protocols and capture and store their own data. The lack of a coordinated approach to clinical trials research in emergency settings has slowed the development of actionable information, which has in turn delayed the availability of vaccines, therapeutics, and diagnostics; and may also impede the tracking of the outbreaks themselves. Without some mechanism to coordinate and organize research on a larger scale in an emergency setting, researchers and decisionmakers are left with a series of relatively small, often inconclusive studies, and assembling data for larger-scale analysis is challenging. In addition, and very significantly, our current approach to clinical research in the emergency setting excludes many patients and health care providers in underserved areas, and has contributed to a lack of diversity among clinical trial participants and among the investigators who lead clinical trials.

The National Biodefense Strategy calls for the U.S. government to maintain and build upon the domestic clinical trials infrastructure, with the addition of international sites as appropriate, to ensure readiness to "expedite the evaluation of safe and effective vaccines, therapeutics, and diagnostics for all segments of the population during a nationally or internationally significant biological incident." [1] In addition, establishing an emergency clinical trials governance structure,

developing the terms of an Emergency Master Agreement to accelerate response, and identifying a network of available sites are among the key goals towards implementation of AP3.[2] In line with these provisions, OSTP (in partnership with the NSC and other EOP components) is leading an effort to ensure that the U.S. can carry out more coordinated and potentially larger-scale clinical trials in emergency situations. These emergency situations could include emerging outbreaks with epidemic or pandemic potential, even in advance of any declaration of a public health emergency (PHE) under section 319 of the Public Health Services Act. By strengthening U.S. capacity to address such outbreaks and other biological incidents, OSTP's emergency clinical trials effort also aims to build and enhance U.S. clinical research capacity overall.

We seek comment below on potential governance models for the emergency clinical trials effort. One possible approach would include a centralized U.S.-level structure drawing membership from Federal agencies with relevant expertise. Governance functions might include determining when coordinated and potentially large-scale clinical research is needed, including research on countermeasures, to address outbreaks of disease or other biological incidents. As noted above, research on an outbreak or incident may sometimes be needed in advance of any section 319 PHE declaration; we solicit comments below on the criteria that should be applied to determine when emergency clinical research may be needed, and how that determination might be communicated to institutions and clinical trial networks that can participate in carrying out the research.

Another governance function might be to oversee the development of emergency clinical trial protocols, in coordination with stakeholders external to the U.S. government. The trials and other studies needed in emergency settings could vary in complexity. Some might be relatively simple studies designed to measure the scope of an outbreak or the course of a disease, in which the data captured from patients might overlap to a large extent with the data that would be gathered in the course of treatment. Other studies, including those designed to evaluate the efficacy and safety of investigational vaccines, therapeutics or diagnostics, would be more complex and could require more or different data elements from those that would be captured in the course of standard medical treatment. In some cases, study designs used in connection with prior outbreaks could provide useful models for developing protocols to address a new emergency. We request comment below on how a governing entity could best work with stakeholders to develop emergency clinical trial protocols.

We also seek comment below on how emergency clinical trial data should be managed to facilitate researchers' access to data and the analysis of results across a range of participating sites. One potential model would be to collect data from emergency clinical trials in a centralized data repository or small set of repositories, with a central biorepository for biospecimens collected during trials.

In order to ensure that coordinated, large-scale clinical trials can be carried out in the event of an emergency, OSTP seeks comment on how best to identify institutions and networks that have an interest in participating in these studies, and how to create or enhance incentives for them to participate wherever possible. In particular, OSTP seeks comment on how to ensure that trial sites in underserved areas are included, and how to increase diversity both among study participants and among the investigators who lead trials to completion. We also solicit feedback below on how to

identify an adequate number and distribution of clinical trial sites, including trial sites located outside of the U.S. This could include sites that may currently be affiliated with a U.S.-based trial network, as well as other international sites. We would appreciate receiving comments on how the domestic emergency clinical trials effort overall can be designed to coordinate with international research and preparedness initiatives.

We are aware that in advance of an outbreak or other emergency, there may be value in having networks and sites begin carrying out clinical trials to create a "warm base" of clinical research capacity. "Warm base" is a term used to refer to studies that not only gather data under a particular clinical research protocol, but also serve the function of keeping trial sites in a state of readiness to undertake additional or future research. "Warm base" studies could address infectious diseases such as influenza, or other medical conditions that are of interest to researchers and communities, such as cancer and heart disease.

To participate in a clinical trial, a site needs to have staff familiar with applicable regulatory requirements and with the appropriate procedures for collecting data and submitting it to a study sponsor. When "warm base" research is initiated, site staff have an opportunity to gain familiarity with these procedures. "Warm base" research is a way to expand the number of sites that are able to participate in clinical trial research, which builds U.S. clinical trial capacity overall while enlarging the network of sites that can be available to carry out emergency clinical trial research when the need arises. We request comment below on a variety of issues related to "warm base" research, including disease areas that might be targeted and how "warm base" research can be implemented to provide targeted training for trial sites, as appropriate to staff roles. Given OSTP's goals of increasing diversity among clinical trial participants and among investigators, and of increasing capacity for clinical research in underserved areas, we are particularly interested in how those goals might be served through the implementation of "warm base" research.

In recent emergency settings, we have seen that the launch of clinical trials across separate institutions or networks can be delayed by the process of coming to agreement on certain key issues, such as data sharing and the publication of results. We seek comment below on the possibility of developing a framework of key terms that can be developed in advance of an emergency and integrated into clinical trial agreements for emergency clinical trials when needed. For purposes of this RFI, we refer to such a framework as an "Emergency Master Agreement." The goal of an Emergency Master Agreement would be to shorten the time it takes to get emergency clinical trial research started across a range of sites, by facilitating agreement on key terms in advance. Certain basic terms could be relevant for any coordinated or large-scale emergency clinical trial, such as provisions that allow data gathered under common protocols from a range of sites to be collected and made readily accessible to researchers beyond the institutions where the trial was conducted. Other basic terms might include central management of biospecimens and the use of a single Institutional Review Board (IRB). In addition to these basic, core terms, an Emergency Master Agreement could include additional terms that might only be needed for certain types of study protocols (*e.g.,* if an investigational agent is being tested). We solicit input below on a range of issues related to the potential creation of an Emergency Master Agreement.

From a technical perspective, OSTP is also seeking input on how best to operationalize both protocol distribution and data capture in a forthcoming RFI.

Information Requested: Respondents may provide information for one or as many topics below as they choose.

1. Governance for emergency clinical trials response.

a. Descriptions of models that could be used to establish a U.S.-level governance structure for emergency clinical trials. As noted above, one possible approach would be a centralized U.S.-level structure drawing membership from Federal agencies with relevant expertise.

b. Criteria that should be applied in determining when coordinated and potentially large-scale clinical research is needed to address an outbreak of disease or other biological incident, including signals or indicators that should be taken into account.

c. Once a need for emergency clinical research is determined, factors relating to the outbreak or incident (*e.g.,* scope, location, severity) that should be considered in determining what types of studies are needed.

d. Methods for communicating the decision to begin emergency clinical research to institutions and clinical trial networks that can participate in carrying out the research.

e. Mechanisms for tracking institutions, networks and sites that might be able to participate in emergency research, to ensure adequate potential for enrollment and adequate geographic coverage, domestically and internationally.

i. Criteria for establishing a target number and location of sites needed to support clinical trials in case of emergency.

f. Procedures whereby the U.S. Government, together with external stakeholders, could oversee the development of clinical trial protocols and, where appropriate, the selection of investigational agents. It would be particularly helpful to get input on whether there is a role for public-private partnerships in this context.

g. Best practices, including "quality by design" principles, for designing trials so that they capture the data needed without unnecessary complexity that can complicate execution.

h. Best practices for designing trials that can enroll vulnerable populations, such as the pediatric population, as needed in particular circumstances.

i. Optimal ways to manage interactions with domestic and international regulatory bodies.

j. Appropriate entities to handle projecting and tracking enrollment at study sites, monitoring the progress of clinical trials, and data management; whether existing entities could be engaged or adapted to carry out these functions for coordinated, large-scale emergency clinical trials.

k. Appropriate ways to structure a data repository and a biorepository for emergency clinical trial data and specimens. As noted above, one potential model would be to collect data and

biospecimens in centralized repositories. We would also appreciate input on whether existing entities could be engaged or adapted to handle these repository functions.

l. Criteria that should be applied to govern researchers' access to emergency clinical trial research data.

2. Identifying and Incentivizing Research Institutions and Networks; Building Diversity and Equity.

a. Methods for identifying institutions and sites that may have an existing interest in or familiarity with emergency clinical trial research. This might include those that currently receive government funding, those with a focus on infectious disease research, and/or those that have worked with CROs.

b. Effective ways to increase diversity among study participants and investigators, and to expand clinical research sites into underserved areas. It would be helpful to get input on whether and how the following approaches could be useful:

i. Community outreach.

ii. Use of decentralized clinical trial (DCT) design elements, or other innovative approaches such as trials conducted at the point of care.

iii. Use of technological innovations, such as digital health technologies (DHTs), that would allow remote participation or otherwise limit the need for participants to travel.

iv. Building on existing programs that target diversity in clinical research, including initiatives within research institutions and public-private collaborations.

v. Leveraging the networks and community access of retail chains, including retail pharmacy chains.

vi. Leveraging community-based care networks such as Practice-Based Research Networks (PBRNs) and Federally Qualified Health Centers (FQHCs).

c. Incentives that can be identified or enhanced to encourage participation in emergency clinical trial research.

i. As described above and in the forthcoming RFI on data capture for Emergency Clinical Trials and Data Collection Pilot, we are seeking information on how to create a pilot program enabling clinical trial data collection across a wide variety of trial sites that is easy for health care providers to use and can be scaled up for use in emergency research settings. It would be helpful to receive comments on whether the opportunity to participate in such a pilot could create an incentive for institutions and sites to participate in emergency clinical research studies.

d. Once interested institutions or networks are identified,

i. Effective ways to recognize and communicate their commitment to emergency clinical research to the health care community and to the public.

ii. Information that should be collected from interested sites, for example by means of a short questionnaire to assess characteristics of patient population, level of training that would be required, etc.

e. The best ways to provide training in clinical trial practice (including regulatory requirements such as Good Clinical Practice (GCP)) where needed, targeted as appropriate to staffs' roles, including staff at sites that may not have participated in clinical trials previously.

3. "Warm Base" Research.

a. Disease areas that should be targeted in protocols for "warm base" clinical research. It would be helpful to get comments on:

i. Disease areas that are most relevant to communities, including underserved communities and those that may have little experience with participating in clinical research.

ii. The extent to which "warm base" research should target infectious disease, versus other conditions such as cancer, heart disease, or rare disease; and the size or scope of site networks that would be needed to study various conditions.

b. How "warm base" research could best be implemented to provide training to sites that are inexperienced with clinical trial research, and to create a basic level of surge capacity at the staff level for emergency clinical trial research. We would appreciate input on other training mechanisms that could be used as well.

c. Whether "warm base" research could be appropriately supported as

i. A demonstration project with commercial partnership.

ii. A public-private partnership.

iii. An agency-funded program.

4. Emergency Master Agreement.

a. Basic terms that might form part of an Emergency Master Agreement, including the following.

i. *Data collection and use,* including ownership of the study data and biospecimens; entities that have the right to collect, store, and use the data and specimens; banking of biospecimens for further research.

ii. *Publication/accessibility of trial data,* including availability of data prior to publication and publication rights.

iii. *Use of a single IRB* across all participating trial sites. As a related point, it would be helpful to get feedback on whether an IRB should be established that is primarily devoted to emergency clinical trials.

b. Additional terms for an Emergency Master Agreement that could be added or modified depending on the complexity of the protocol, and on other factors such as whether a private sector sponsor or an investigational agent is involved. It would be helpful to have input on terms such as the following:

i. Confidentiality.

ii. Patents/intellectual property.

iii. Control of study drug.

iv. Indemnification.

v. Compensation for injury.

c. The best ways to get the input of research institutions, clinical researchers, community groups, and other key stakeholders on the content of Emergency Master Agreement terms.

d. Approaches to facilitating stakeholders' understanding and adoption of the Emergency Master Agreement framework.

i. Any models for such adoption in related areas, such as the NCATS SMART IRB Platform.

5. Identifying viable technical strategies for data capture; gathering information about a potential data capture pilot. This topic will be the subject of a separate RFI on data capture.

6. International coordination and capacity.

a. Designing the overall domestic emergency clinical trials effort in a way that coordinates with international clinical research efforts. It would be helpful to receive comments on how to facilitate the participation of foreign-run clinical trial networks and other foreign bodies in coordinated, large-scale emergency clinical trial protocols initiated by the U.S.

b. Methods for identifying international sites that might be available to participate in emergency clinical trials, including international sites associated with U.S.-run networks as well as foreign-run international sites.

c. Overcoming regulatory barriers that delay expansion of U.S. trials into international sites, or otherwise interfere with clinical research across borders.

d. The best way to track the clinical trial research initiatives being pursued under the G7 Trials Charter and Quad leaders' commitment to pandemic preparedness, and to harmonize U.S. emergency clinical trials efforts with these international initiatives.

Dated: October 19, 2022.

Stacy Murphy, Operations Manager.

Footnotes

1. 2022 National Biodefense Strategy for Countering Biological Threats, Enhancing Pandemic Preparedness, and Achieving Global Health Security (October 2022), section 4.1.4.

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2. First Annual Report on Progress Towards Implementation of the American Pandemic Preparedness Plan (September 2022), at 22-23.

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[FR Doc. 2022-23110 Filed 10-25-22; 8:45 am]

BILLING CODE 3270-F1-P

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Submitted electronically

December 27, 2022

Dr. Arati Prabhakar
Director
Office of Science and Technology Policy
The White House
Washington, DC 20502

Re: Request for Information on Clinical Research Infrastructure and Emergency Clinical Trials - Federal Register Document Citation 87-FR-64821

Dear Dr. Prabhakar,

FasterCures is pleased to respond to your Request for Information on clinical research infrastructure and emergency clinical trials. FasterCures strongly believes that it is critical in this moment to make real change and transform the way that local institutions conduct clinical research so that it better represents the diverse communities that comprise the American population. Because of this, we are gratified that this concept is being seriously considered.

As you may know, FasterCures, a center of the Milken Institute, is driven by a singular goal: to save lives by speeding scientific advancements to all patients. With an independent voice, FasterCures is working to build a system that is effective, efficient, and driven by a clear vision: working with our partners to build a patient-centric system where science is accelerated, unnecessary barriers are overcome, and lifesaving and life-enhancing treatments get to those who need them as rapidly and as safely as possible.

Since 2020, FasterCures has engaged in activities to further understand changes to clinical research in response to the COVID-19 pandemic and the growing impetus to prioritize community needs and access to clinical research. As we are all acutely aware, the COVID-19 Public Health Emergency (PHE) revealed the heavy price of a lack of a comprehensive community-based research system. The pandemic also saw the development of many best practices from organizations, networks, and partnerships that are now leading the way in community-based clinical research. These advances offer many ideas that could contribute to a government-led, coordinated clinical trials system to respond to outbreaks and emergencies. Below we explore ways to expand upon those existing best practices as well as identify common infrastructure gaps and potential solutions to strengthen community-based research.

1

Governance for Emergency Clinical Trials Response

Descriptions of models that could be used to establish a U.S.-level governance structure for emergency clinical trials

An essential next step to establish a US-level governance structure for emergency clinical trials is to **coordinate government-funded networks and sites**. The federal government currently supports multiple trial networks and sites across many federal agencies that have reach into diverse communities and populations. The National Institutes of Health (NIH), the Department of Defense (DoD), the Veterans Health Administration, the Health Resources and Services Administration's (HRSA) Health Center Program, and the Centers for Medicare and Medicaid Services' (CMS) Minority Research Grant Program all fund networks.

A federated approach linking other private health-care systems and networks and establishing a better view across the existing infrastructure is needed. The NIH's Clinical Trial Capacity Inventory and geotracking tool—established during the pandemic—should be maintained and expanded to involve other government-funded health systems, such as the Department of Veterans Affairs (VA), the DoD, and the Federally Qualified Health Centers. Additionally, data definitions and data collection tools need to be aligned to create one common approach among the NIH, Food and Drug Administration (FDA), CMS, HRSA, and other relevant agencies. This alignment will help address the current landscape of differing expectations, difficult reporting, and challenging data aggregation.

Priority setting is another essential aspect of a US-level governance structure for emergency clinical trials. A national authority should be tasked with identifying useful networks, policies, and resources utilized during the COVID-19 PHE and enable their use against varying public health priorities without the need to declare a formal emergency.

A cross-agency working group guided by representatives of diverse communities and researchers should be convened to establish a plan to train and keep community-based research sites engaged. Researchers and companies supporting commercial clinical trial sites should be included in this group to maximize the potential reach into communities and support of community-based research sites. This prioritization must also be informed by increasing and improving data monitoring and advancing analytics to identify patterns of disease in communities. This may lead to other threats, such as cancer, opioids, or suicide, being deemed a PHE and deploying existing infrastructure and resources to address those problems similarly to the COVID-19 pandemic. Finally, Congress should ensure that agencies are directing funding toward such research priorities.

Procedures whereby the U.S. Government, together with external stakeholders, could oversee the development of clinical trial protocols and, where appropriate, the selection of investigational agents

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The COVID-19 pandemic saw an unprecedented scale and speed of collaboration between public and private entities to tackle challenges presented by the PHE. The federal government partnered with companies and research institutions to identify products in the pipeline that could address the new threat. A prime example is the US National Institute of Allergy and Infectious Diseases partnering with Moderna to develop a vaccine, a longtime collaboration that bore fruit in a critical moment.

Another key example is the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) public-private partnership. This partnership brought together US federal health agencies, the European Medicines Agency, and several biopharma companies, academic institutions, and philanthropies to develop a research strategy that would prioritize and quicken the development of treatments and vaccines. By bringing together all these stakeholders, ACTIV has improved the sharing of preclinical resources, set up master protocol trials to test candidates, and maximized existing trial infrastructure. The US government should document, characterize, and quantify the benefits of these partnerships as well as continue to explore and deepen its collaborations with external stakeholders. Existing partnerships such as ACTIV should be directed toward other high-priority, unmet health needs, and Congress should invest in the important platforms and tools created through pandemic-era public-private partnerships.

Best practices, including "quality by design" principles, for designing trials so that they capture the data needed without unnecessary complexity that can complicate execution
Many administrative and regulatory protocols burden clinical trial sites and investigators, creating unnecessary complexity and slowing the research and discovery process. These include contracting, the Institutional Review Board process, consent requirements, and more. Small and less experienced research entities are not the only groups bogged down by these complexities; more experienced government research agencies, such as the VA, face slow execution of interagency agreements, even in the face of a PHE.

Other complicating factors include differing state and institutional requirements for research conduct and administration. The COVID-19 Evidence Accelerator, an initiative launched by the Reagan-Udall Foundation for the FDA in partnership with Friends of Cancer Research, provides an opportunity for organizations to work through challenges such as real-world data (RWD) standardization, interoperability, and methods. This initiative should remain active as a way for stakeholders to advance RWD/real-world evidence (RWE) and address data collection issues.

Although randomized controlled trials have long been considered the "gold standard" in product evaluation and approval, recent years have exposed their limitations. Those limitations include accurately capturing the likely performance of treatment approaches in actual practice, and the associated complexities and requirements have led to a wall between the systems of clinical research and clinical care when it comes to data, personnel, and processes, contributing to higher costs and longer timeframes. To solve some of these pressing challenges, the federal government must support, expand, and link clinical trial networks and move toward pragmatic trials to quickly generate RWD/RWE. This includes improved methods for collecting data that are "lightweight" for clinicians and take place where patients are regularly receiving their care.

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This support also includes running larger, simpler trials and maintaining and building upon COVID-19 trial infrastructure, such as platform trials and networks, to incentivize research on topics of high unmet need. These trials must be interoperable and readily able to link in networks of networks or pivot rapidly to areas in urgent need of greater capacity. These pragmatic trials may not collect all possible data, but, especially when operating complementary to more detailed, costly studies, will provide important, and otherwise unknown, findings.

Best practices for designing trials that can enroll vulnerable populations, such as the pediatric population, as needed in particular circumstances

Best practices for trial design specifically to include vulnerable populations can be pulled from the NIH's Community Engagement Alliance (CEAL) and COVID-19 Prevention Network (CoVPN). During the pandemic, CEAL leveraged relationships formed and lessons learned from the All of Us Research Program to engage communities that were most impacted. The initiative successfully reduced vaccine hesitancy, improved vaccine uptake, and increased participation of racial and ethnic minority populations in COVID-19 clinical trials**.**

CoVPN was created on the foundation of the HIV trials networks that have a strong history of engaging local communities. The program helped enroll in clinical trials for COVID-19 medical countermeasures people with underlying medical conditions, people with greater chances of exposure at their jobs, and people from racial and ethnic groups disproportionately impacted by the pandemic. CoVPN also successfully improved the process of designing, implementing, and analyzing vaccine trials; streamlining the development of protocols maintaining input from diverse stakeholders; and setting new statistical standards for the field. These two initiatives demonstrated the importance of continuous engagement with vulnerable communities to foster trust during the clinical trial process.

Additional best practices include bringing patient advocates and underrepresented community members into the trial design process as co-designers to ensure the research outcomes align with a broader impact and benefit. By developing relationships with community leaders and local health centers, academic institutions and principal investigators can address the barriers that limit patients' participation in trials. Finally, developing inclusive patient and research navigation programs created by community health workers, lay health workers, and health educators can help support capacity building, outreach, cultural competency, and health literacy in clinical trials.

Identifying and Incentivizing Research Institutions and Networks; Building Diversity and Equity

Community outreach

Patients bring unique expertise and knowledge to the R&D process due to lived experience, and engaging them into the decision-making processes in the earliest stages would prove beneficial. Community-based participatory research is a growing discipline, and utilizing community

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outreach to engage diverse populations in research is essential to developing treatments and cures of value to all communities. It is essential to focus on community engagement in the early stages of the R&D process to obtain feedback on protocol design, subject eligibility/ineligibility criteria, and outcome measures. As opposed to viewing patients as subjects in research, this approach holds deep respect and value for their contributions and treats patients as participants in the research process.

Community outreach opportunities are numerous in historically underrepresented communities, especially among community-based organizations such as the National Black Church Initiative, Historically Black Colleges and Universities, and Minority Serving Institutions, and policy organizations, such as the National Minority Quality Forum. The first and most important step to community outreach, however, is building trust with communities. This process is long overdue and will take time and prioritization. As was the case during the COVID-19 pandemic, successful recruitment in minority communities includes direct engagement and physical outreach to target populations. A successful community outreach campaign must also address hesitancies, mistrust, and fear at all levels in the clinical trial process in a sincere and authentic manner.

Non-traditional workers, such as community health workers or health educators, have a significant role in supporting these community outreach programs. This broadening of the workforce can ensure communities are consistently and meaningfully represented in a clinical trials network and improve its overall reach and preparedness. Such a critical workforce needs predictable funding, and sustainable payment and reimbursement models for this type of workforce are needed.

Use of decentralized clinical trial (DCT) design elements and technological innovations that allow remote participation

A central way to involve diverse populations in clinical trials is through the use of large and simple trial designs. Decentralized clinical trials became a standard during the pandemic and will likely become a mainstay as it allows researchers to meet patients where they are. An estimated 70 percent of potential trial participants live more than two hours away from a trial site.[1] Decentralization creates opportunities for trials to have a much broader reach. Remote and digital tools are essential to decentralizing trials and engaging underserved populations. During the pandemic, the FDA allowed many clinical trials to utilize decentralized and remote approaches such as remote check-in with participants (by phone or video), shipment of study products to patients' homes, and the use of mobile devices.

The use of decentralized trials and remote tools during the pandemic relied heavily on flexibilities put in place during the PHE. Actions need to be taken to preserve that progress and the use of those tools to continue their valuable contribution to clinical trials. Hindrances to their continued use include policy barriers such as cross-state licensing restrictions on

[1] Milken Institute, 2022. Building Community-Based Infrastructure for Inclusive Research: Lessons from the Pandemic for Federal Action.

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physicians, as well as inertia and risk aversion by sponsors. However, researchers must be careful not to disenfranchise underserved communities through decentralized trials and remote tools, despite their usefulness. Although these methods aim to engage more communities, they may contribute to further barriers for patients who lack the technology required to participate.

Building on existing programs that target diversity in clinical research, including initiatives within research institutions and public-private collaborations

Despite an NIH mandate in 1993 to increase the inclusion of more racial and minority participants in federally funded research, little progress has been made. Early in the pandemic, most states did not have mechanisms for reporting data on race/ethnicity with regard to COVID-19 cases or deaths. Now the majority of states are reporting these data, but they remain incomplete.

Research institutions and public-private collaborations have made strides in addressing diversity in clinical research and can serve as examples to build upon. Many organizations have invested in new positions to address diversity, equity, and inclusion. Some are announcing specific investment plans, such as one that is making a $300 million investment to improve diversity across their own programs, including a five-year plan focused on hiring practices, clinical trial recruitment, raising disease awareness, and access to care. Others have partnered directly with minority-serving medical schools to better understand and address health inequities in minority communities using fit-for-purpose data resources. The NIH has initiated a program working with community partners in its network to share public health information and encourage participation in COVID-19 therapeutic and vaccine trials.

Several elements came together during the first stages of response to COVID-19 that increased engagement of diverse sites and patients, including:

- Identification of existing government-funded research infrastructure and community-engaged researchers to participate in initiatives such as CEAL and CoVPN;
- Federal action by agencies, including the FDA and CMS, to enable and encourage the use of more decentralized and remote methods and tools to conduct trials during the pandemic (many of which will explicitly be terminated at the end of the PHE);
- Federal leadership in directing sponsors of COVID-19 vaccine trials to achieve greater diversity in the study population; and
- Leveraging an arm of the RADx program to accelerate innovation in COVID-19 diagnostics to focus specifically on understanding and addressing the needs of underserved populations.

Despite individual organization plans to institute change and facilitate more diverse clinical trials, there is a need for more cohesive plans and leadership to set priorities and hold people and groups accountable and encourage systems change. Government and philanthropy can spur commitments, collect data, and issue report cards on areas of success or in need of improvement.

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Leveraging the networks and community access of retail chains, including retail pharmacy chains

Supporting community research requires the development of new pathways and ways to engage people at all stages of the research pipeline. Examples include involving pharmacists, PhDs, and research coordinators. The longstanding MD-centric clinical trial investigator model needs to be rethought, and more "boots on the ground" actors, such as pharmacists and clinical hospitalists, need to be incorporated into clinical trial functions. Additionally, there is a need for greater infrastructure and support for pharmacy, specifically for inpatient clinical trials. Investigational pharmacy is a unique field, and many trial sites do not have support of this kind. To engage partners such as retail pharmacies, local imaging and diagnostics labs, and mobile nurses, it is imperative to clarify and modernize regulations.

Some progress has been made in this area, with large pharmacy chains and independent community pharmacies alike serving as instrumental components in providing access and engaging historically underrepresented groups in our country's pandemic response.[2] Large pharmacy chains and retailers are also now entering the clinical research space.[3] These examples are promising indicators of the potential for pharmacies to improve access to care and research for all populations.

"Warm Base" Research

Disease areas that should be targeted in protocols for "warm base" clinical research

"Warm base" clinical research should address conditions that are disproportionately experienced by underserved and underrepresented populations. Black, Latinx, and Native Americans are more likely than White Americans to suffer from chronic conditions such as diabetes, heart disease, and asthma. Rural populations face many challenges accessing clinical trials and have long been underrepresented in research due to the lack of nearby locations conducting research and the limited involvement of community providers. Setting up clinical research infrastructure in community-based settings presents a unique opportunity to engage more diverse populations in research.

Decisions about what disease areas and research to prioritize for such a "warm base" network are complex and have far-reaching implications for many people and communities. A cross-stakeholder **Grand Challenges Working Group—**made up of representatives from across the Department of Health and Human Services and other federal-supported biomedical research agencies as well as non-federal representatives of patients, industry, public health experts, and others as needed—could prioritize research challenges to support via this infrastructure. The working group could consider high public health needs, high health-care costs, and low innovation activity as criteria for prioritizing disease categories.

[2] One example of this analysis can be found https://www.sciencedirect.com/science/article/pii/S1544319122002795

[3] See, for example: https://www.reuters.com/business/healthcare-pharmaceuticals/walmart-compete-with-walgreens-cvs-recruiting-clinical-trial-subjects-2022-10-11/

7

How "warm base" research could best be implemented to provide training to sites that are inexperienced with clinical trial research, and to create a basic level of surge capacity at the staff level for emergency clinical trial research and "warm base" research supported as a public-private partnership

An essential component for "warm base" research is consistent funding to develop new research infrastructure, as well as maintain existing infrastructure and personnel. Additionally, preexisting relationships may provide the greatest path to establish stronger research opportunities in community-based settings and move forward quickly during a PHE. This may include involvement from academic or commercial centers to mentor and support community health care facilities that are frequently overburdened or have limited resources for research. Successful networks and partnerships that largely led the pandemic response, including ACTIV and CoVPN, had strong foundations of existing clinical trial infrastructure and stressed the importance of clinical trial networks that can rapidly engage to support the coordination of research during a PHE.

In addition to mentorship and partnership, there are opportunities to creatively support community sites such that they are prepared and enthusiastic to participate in research. A growing commercial sector is working to address gaps felt by community-based sites, a layer between traditional contract-research organizations and the sites themselves. Companies in these sectors are rolling out platforms that help community hospitals anticipate upcoming research and stabilize their research pipelines or working to embed clinical research personnel in community hospitals as a type of core service akin to onsite clinical labs managed by external companies. These possibilities suggest a path to enable consistent and seamless integration of community sites into a larger research network.

Thank you again for the opportunity to offer our input. We are happy to discuss these ideas further and help OSTP advance any ideas shared in this response.

Sincerely,

Esther Krofah
Executive Vice President of Health
Executive Director, FasterCures and Center for Public Health
Milken Institute

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December 27, 2022

Dr. Arati Prabhakar, Director
White House Office of Science and Technology Policy (OSTP)

Subject: Request for Information (RFI); Clinical Research Infrastructure and Emergency Clinical Trials: 87 FR 64821

Walgreens is pleased to submit comments to the White House Office of Science and Technology Policy (OSTP) on its Request for Information (RFI) on Clinical Research Infrastructure and Emergency Clinical Trials ("Emergency Clinical Trials"). We comment primarily on topic #2, "identifying and incentivizing research institutions and networks; building diversity and equity." Walgreens is committed to addressing the larger healthcare inequities, recently made more evident and pressing by the COVID-19 pandemic and is uniquely situated to provide holistic, community-based responses to these issues. We continually challenge ourselves to identify what more Walgreens can do to improve care in the communities that need it most and, prominent among these opportunities, is access to clinical trials.

Walgreens is an integrated pharmacy, healthcare and retail entity operating nearly 9,000 locations across America and serving approximately 9 million customers each day. At the center of Walgreens consumer-centric healthcare strategy is our newest business segment, Walgreens Health, a technology-enabled care model that leverages Walgreens strengths and assets, including trusted consumer relationships and community presence, national scale, care teams and partnerships with providers across the country. This locally delivered platform will create better experiences for consumers, improve health outcomes, lower costs, and address health equity.

Clinical research and real-world evidence play an important role in the advancement of modern medicine and patient empowerment. Yet, two-thirds of patient recruitment to support US drug approvals is done outside of the US, where laws, regulations, and standards differ[1]. Further, half of the volunteers in clinical trials are regarded as 'higher income' despite representing only 16% of the general U.S. population. Thirty-eight percent of Americans are 'lower middle income,' but represent only 14% of clinical trial participants[2]. Given 78% of Americans live within five miles of a Walgreens and nearly half of these locations are in socially vulnerable areas, our physical presence can reduce or eliminate the barrier of distance to research sites and reach people where

[1] Berman-Gorvine M. Two-thirds of trial subjects for drug approvals are outside the U.S. WCG. Centerwatch, November 16, 2020. Available from: https://cms.centerwatch.com/articles/25116-two-thirds-of-trial-subjects-for-drug-approvals-are-outside-the-us

[2] Kaiksow FA, Carter J. National Academies Press, 2022.
A comprehensive literature review addressing the range of factors that prevent inclusion in clinical trials and research. Available from: https://nap.nationalacademies.org/resource/26479/Kaiksow_Lit_Review-Factors_that_Prevent_Inclusion_Clinical_Trials_and_Research.pdf

they live. Through digital and in-person outreach, we can engage, educate, and empower communities to learn about clinical research while actively listening to communities who may not fully understand the relevance of drug development in the context of their care. We are seeking to address the challenges within clinical trial execution and research and improving the overall experience by rapidly scaling three portfolio-integrated, patient-centric service lines: 1) insights-driven patient recruitment; 2) bringing trials to patients; and 3) delivering real-world evidence and informatics.

Walgreens applauds OSTP's efforts to ensure that coordinated and large-scale clinical trials be efficiently carried out across a range of institutions and sites, particularly leveraging the networks and community access of community pharmacy chains, to address outbreaks of disease and other emergencies. We share OSTP's concern with a lack of a coordinated approach to clinical trials that became apparent during the early stages of the COVID-19 pandemic. Specifically, we recognize that gaps in the current clinical trial structure, and inability to leverage the entire health care ecosystem in the clinical trial process leads to general lack of participation, lack of diversity among participants and health care providers, lack of community outreach and partnership, and disparate research protocols and data capture. These same issues lead to a lack of trust from both a patient and provider point of view, and are made more significant in our most vulnerable populations, including for those suffering chronic and polychronic diseases. Since the hope and potential envisioned through clinical trials is diminished for some populations[3], ready access and convenient and equitable patient engagement must be central to next-generation clinical trial enrollment and retention success. Only 7 out of 100 interested patients complete a clinical trial and the dropout rates are ~20% among those who enroll[4]. This is not from a lack of trying. Trial sponsors spend $19B annually on recruitment, yet ~50% of trial sites fail to meet enrollment goals[5]. Potential losses caused by trial delays are $600K - $8M/day due to recruitment and retention issues[6]. This leads to a misappropriation of resources that not only stifles the prospects of the candidate therapy, but also affects the viability and sustainability of the drug pipeline. In the early days of the pandemic, access to real-world evidence proved to be a critical tool in understanding and identifying the treatment approaches showing promise in improving outcomes for patients infected with SARS-CoV-2. As vaccines were developed and quickly administered under FDA's Emergency Use Authorizations, through community partners like Walgreens, this evidence was utilized to understand important safety side effects, and incidence rates as well as effectiveness in diminishing the severity of COVID-19 symptoms. Today, the study of patients suffering from long COVID continues through the use of current and demonstrated evidence. With such a strong presence in the community, Walgreens is well suited to scale a response to a pandemic but also measure through real-world evidence and data, the impact to individual patients.

[3] According to FDA's 2021 data snapshot on diversity and inclusion among trials, 75 percent of participants enrolled in trials were White. Among 32,000 patients participating in these trials, just 11 percent were Hispanic, 8 percent were Black, and 6% were Asian. 2021 Drug Trials Snapshots Summary Report, Center for Drug Evaluation and Research's (CDER's), U.S. Food and Drug Administration (FDA), Published 05/16/2022

[4] https://forteresearch.com/news/infographic/infographic-retention-in-clinical-trials-keeping-patients-on-protocols/

[5] https://www.prnewswire.com/news-releases/outcome-health-introduces-clinical-trial-solution-to-boost-patient-recruitment-300395346.html

[6] http://www.pharmafile.com/news/511225/clinical-trials-and-their-patients-rising-costs-and-how-stem-loss

Pharmacies such as Walgreens can offer the following benefits to the clinical trial process:

- **Awareness:** A broad geographic reach, opportunities to engage with patients where they live, meaningful community engagement[3], and existing relationships with trusted pharmacists lead to an increased number of potential participants made aware of the trials they may qualify for and enable them to complete screening and enrollment activities in their local communities. This can lead to accelerated recruitment.
- **Access:** Retail pharmacies can increase access to clinical trials by leveraging consumer retail and prescription insights and provide a reliable point of contact for study participants who require support during the trial journey. Using decentralized clinical trial elements (e.g. telemedicine, electronic Informed Consent, electronic Clinical Outcome Assessments, electronic Patient Reported Outcomes), we offer convenience for patients. As we continue to develop our patient registry for clinical research, we will be able to quickly identify participants for research,
- **Diversity:** By diversifying the pool of participants who sign up for clinical trials, retail pharmacies facilitate trials with clinical endpoints more relevant for a broader group of patients (e.g., rural access, women, and minorities).
- **Digital:** The activation of communities through digital tools can provide potential participants with additional methods to engage in clinical research processes beyond traditional recruitment strategies. For example, combining in-person Community Advisory Boards with digital focus groups to crowdsource feedback can enhance the quality of study design and improve retention. By building a continuum of community engagement between volunteers and staff, we strengthen the existing bond of trust.
- **Flexibility:** Retail pharmacies can bring more processes out of the clinical trial site to more convenient locations such as the local pharmacy or home to reduce costs of burdensome travel, repeated monitoring, and in-person visits. This can lead to improved patient retention and quick access in public emergencies that do not additionally overburden the primary care infrastructure. In addition, we are plan, provider and sponsor agnostic, providing multiple avenues to coordinate across the care industry
- **Operations:** Pharmacies can act as a hub in providing clinical services to clinical trial participants given the frequency of customer interaction and ease of customer contact as compared to others in the clinical trial space.
- **Data:** Real world evidence generation and access to critical information across broad populations can facilitate speedy, informed, decisions in emergency response, test intervention success rates, and help continually improve responses to a particular situation. In addition, our patient registry will provide ample de-identified data to support emergency response efforts.

Patients experience numerous challenges in the clinical trial participation process. Specifically, trials are not designed around participant experience and place significant time, physical, and resource burdens on participants. Patients are often unaware of clinical trials or are afraid to enroll because they may perceive them as risky and complex or because they may have a general lack of trust for the research process. When a patient encounters a clinical trial listing, they can find it hard to decipher, particularly eligibility criteria and type of intervention. Additionally,

compensation, time commitment, and potential risks are often not clearly stated. Language and cultural differences are often barriers for racial and ethnic minorities. Finally, interested patients start by contacting a site or research coordinator, sometimes with little success. The screening process can be very slow and cumbersome with medical records often being difficult to access and visits to faraway sites normally required.

Walgreens trusted pharmacy staff are especially well positioned to remove these barriers to clinical trial access. Pharmacies are more prevalent and accessible than other healthcare entities because they are located within and intended to serve communities directly. Approximately 90% of all U.S. residents live within five miles of a community pharmacy. High-risk Medicaid patients visit their local pharmacy about 35 times per year[7], and pharmacy visits by Medicare patients significantly outnumber primary care encounters (13 pharmacy visits to 7 primary care encounters per year), with the difference in rural areas being even more profound (14 compared to 5)[8]. Additionally, the ability of pharmacies to reach the most underserved populations has never been more apparent than during the COVID-19 pandemic. Walgreens rose to this unprecedented challenge by educating the public to encourage vaccine adoption, making services available to our most vulnerable populations, including holding community and senior living facility vaccination clinics, providing digital engagement to make vaccination appointments safe and easy, and we provided and leveraged data to support public health in new ways. Walgreens pharmacies have deployed the following strategies to enhance equity throughout the COVID-19 response and vaccination campaign that highlight touchpoints for improvement in public education and access to clinical research:

- Pharmacies have deployed data-driven approaches to achieving enhanced equity, leveraging the CDC's Social Vulnerability Index (SVI), information on health professional shortage areas, and medically underserved population measures to help focus efforts in communities facing the greatest challenges.[9] Half of pharmacy COVID-19 vaccination sites are located in areas with high social vulnerability.[10] Pharmacies are home to more than 20,000 COVID-19 testing sites nationwide, and 70% of which are in areas with moderate to severe social vulnerability.[11]
- Community pharmacies have provided COVID-19 vaccinations for homebound individuals, conducted pop-up clinics, and partnered with schools, community centers, places of worship, employers, community leaders, faith-based organizations, and

[7] Gaskins RE. Innovating Medicaid: the North Carolina Experience. https://www.ncbi.nlm.nih.gov/pubmed/28115558

[8] Berenbrok LA, et al. Evaluation of Frequency of Encounters With Primary Care Physicians vs Visits to Community Pharmacies Among Medicare Beneficiaries.

[9] Agency for Toxic Substances and Disease Registry. CDC/ATSDR Social Vulnerability Index. Updated November 16, 2022. Accessed December 7, 2022. https://www.atsdr.cdc.gov/placeandhealth/svi/index.html

[10] United States Government Accountability Office. Covid-19 Federal Efforts to Provide Vaccines to Racial and Ethnic Groups. February 2022. Accessed December 7, 2022. https://www.gao.gov/assets/gao-22-105079.pdf.

[11] White House, FACT SHEET: Biden Administration Announces Historic $10 Billion Investment to Expand Access to COVID-19 Vaccines and Build Vaccine Confidence in Hardest-Hit and Highest-Risk Communities. March 25, 2021. Accessed December 7, 2022. https://www.whitehouse.gov/briefing-room/statements-releases/2021/03/25/fact-sheet-biden-administration-announces-historic-10-billion-investment-to-expand-access-to-covid-19-vaccines-and-build-vaccine-confidence-in-hardest-hit-and-highest-risk-communities/.

organizations representing racial and ethnic minority groups.[12] Pharmacies have provided more than 11,000 mobile COVID-19 vaccination clinics across the country.[13]

- Pharmacies have collaborated with rideshare companies, deployed mobile vaccination units, and made every effort to meet people where they are. By redoubling community outreach strategies that have worked well for flu shots, offering appointment times well into the evening hours and on weekends, and working to overcome disparities in technology access, even going door-to-door, pharmacy is able to extend its reach beyond its brick-and-mortar footprint to better serve patients and customers.[14]
- Pharmacies are uniquely situated to supplement new and existing policy efforts to provide virtual access, and in so doing, enable the integration of digital health services.[15]

The pandemic highlighted both the public need for care at their local pharmacies and the many ways in which pharmacies can improve public health. The same tools utilized to address the pandemic can also be called upon to support flexible and engaging research programs. Walgreens provides distinct value as a trusted member of local communities to empower and support patients through the complex clinical trials process. This ability to support patients throughout their health journey will drive better and higher quality patient participation and improve retention rates. Through our assets and partnerships, including our Village Medical at Walgreens primary care practices[16], Health Corner locations focused on preventive and wellness services[17], in-home care, specialty pharmacy and robust digital engagement, Walgreens stands ready to address underrepresentation in clinical trials and improve public health in response to emergencies. Indeed, Walgreens could partner with the agency to facilitate community preparedness and response for any number of emergencies, natural disasters, and failures of infrastructure—something we have had a long history of doing already. Walgreens access to

[12] Centers for Disease Control and Prevention. Stories from the Field: Federal Retail Pharmacy Program for COVID-19 Vaccination. Updated November 29, 2022. Accessed December 7, 2022. https://www.cdc.gov/vaccines/covid-19/retail-pharmacy-program/retail-stories.html.

[13] National Association of Chain Drug Stores. NACDS and 93 other patient, public health and pharmacy groups urge continued access to pandemic-related services. June 7, 2022. Accessed December 7, 2022. Available at: https://www.nacds.org/news/nacds-and-93-other-patient-public-health-and-pharmacy-groups-urge-continued-access-to-pandemic-related-services-at-pharmacies/.

[14] Coppock K. Pharmacies Extending Friday Hours in June to Increase Access to COVID-19 Vaccination. June 10, 2021. https://www.pharmacytimes.com/view/pharmacies-extending-friday-hours-in-june-to-increase-access-to-covid-19-vaccination.

[15] US Department of Health and Human Services. HHS awards nearly $55 million to increase virtual health care access and quality through community health centers. February 14, 2022. Accessed December 7, 2022. https://www.hhs.gov/about/news/2022/02/14/hhs-awards-nearly-55-million-increase-virtual-health-care-access-quality-through-community-health-centers.html#:~:text=media%40hhs.gov-,HHS%20Awards%20Nearly%20%2455%20Million%20to%20Increase%20Virtual%20Health%20Care,technology%20to%20support%20underserved%20communities.

[16] https://news.walgreens.com/press-center/walgreens-and-villagemd-expand-full-service-primary-care-practices-to-las-vegas.htm

[17] https://news.walgreens.com/our-stories/walgreens-100-health-corners.htm

data and digital health capability could be leveraged to provide intervention programs for specific disease states or to identify hot spots for disease activity.

Walgreens has built a strong, flexible and fully compliant operating model for clinical trials and has activated pharmacy locations as Clinical Trial Centers. Moving forward, we will continue to scale and activate more locations, and engage with other trusted community partners focused on meeting patient needs across our footprint so that patients will have easy access to, and confidence in clinical trial participation. We also have established a platform that enables aspects of a digital clinical trial workflow (e.g. telehealth solutions for patient and provider engagement) to serve as a secure and flexible option for patients who require or request remote participation. Finally, we are optimally positioned to offer home health services through CareCentrix[18], our post-acute home care provider, and are establishing a partnership with Uber Health to provide travel services for patients who are unable to travel to our pharmacy stores for their clinical trial visits.

Given that pharmacies are close to home and provide integrated healthcare destinations within the communities we serve, we have an on-the-ground understanding of the local social, economic, and cultural dynamics. This understanding and these relationships help cultivate meaningful connections to better meet healthcare needs, making pharmacies well suited to address barriers to successful clinical trial participation, especially in emergency settings. As such, Walgreens seeks to partner with OSTP to identify and leverage the clinical trial solutions we provide as you seek to coordinate large-scale clinical trials that can be carried out in the event of an emergency. We stand ready to assist in whatever ways we can and encourage OSTP to call on its pharmacy network to empower Americans to live more joyful lives through better health. We appreciate the opportunity to provide comments to this RFI. If we can be of any further assistance, please do not hesitate to reach out at (202) 393-0414 or via email at charley.john@walgreens.com.

Sincerely,

Charley John
Senior Director, Healthcare Policy & Strategy
Walgreens

[18] https://news.walgreens.com/press-center/walgreens-boots-alliance-accelerates-full-acquisition-carecentrix.htm

Congress of the United States
Washington, DC 20515

January 26, 2023

Arati Prabhakar
Director
Office of Science and Technology Policy
1650 Pennsylvania Avenue NW
Washington, DC 20502

RE: Response to Notice of Request for Information on clinical research infrastructure and emergency clinical trials (87 FR 64821)

Dear Director Prabhakar:

As Members of Congress committed to ensuring that advances in vaccines, therapeutics, and diagnostics are available to all Americans during a public health emergency, we applaud your office for leading efforts to create a U.S. clinical trial infrastructure that can better respond to infectious disease outbreaks or other emergency situations. As you embark on this work, we urge you to take steps that will guarantee that the infrastructure prioritizes the inclusion of pregnant women and lactating women in clinical research during times of emergency.

The COVID-19 pandemic demonstrated that our existing system of disconnected research institutions and disparate data systems hindered the development of more immediate diagnostics, treatments, and vaccines for COVID-19. As the request for information notes, the current system also exacerbates the underrepresentation of certain populations in clinical trials in the emergency setting. While many populations are problematically underrepresented in clinical research, pregnant women and lactating women are regularly excluded from clinical trials in both regular and emergency settings.

Patients and their doctors need accurate information about effects of medications during pregnancy and lactation to ensure the best health outcomes for themselves and their babies. Failure to include these populations in clinical research has a significant impact on the care provided to pregnant and lactating women during a public health emergency. Using COVID-19 as an example, pregnant and lactating women were largely excluded from COVID-19 treatment trials.[i] Without data on the safety and efficacy of therapeutics to both the mother and baby, clinicians and their patients had little information to guide treatment decisions. These populations were also overwhelmingly excluded from COVID-19 vaccine trials.[ii] As a result, some patients were reluctant to receive vaccination, even when recommended by clinicians. In the months after vaccines became available to the public, pregnant women were far less likely to be vaccinated than their peers who were not pregnant.[iii] This left expecting mothers without protection during a time when they were more vulnerable to serious illness.

We can and must do better for the more than 6 million Americans who become pregnant each year. They deserve access to the same life- and health-protecting treatments and vaccines during a pandemic as their non-pregnant peers. The Office of Science and Technology Policy (OSTP) should incorporate these unique populations into every aspect of planning for an improved clinical research infrastructure, including:

- Prioritizing pregnant and lactating women in the development of clinical trials protocol;
- Developing best practices for designing trials that incorporate pregnant and lactating women and for recruiting these populations;
- Leveraging existing obstetric clinical trial networks, such as the Maternal-Fetal Medicine Units (MFMU) Network;
- Incentivizing or providing additional financial support to clinical trial sites that enroll pregnant and lactating women with robust patient safeguards; and
- Ensuring that any common Institutional Review Board includes members with expertise in obstetrics and maternal-fetal medicine and documents a justification for excluding pregnant or lactating women from clinical trials based on regulatory requirements outlined the Federal Policy for the Protection of Human Subjects (the "Common Rule").

In addition to the recommendations outlined above, the Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC) has released a series of recommendations and an implementation plan that contains detailed recommendations to advance the inclusion of pregnant and lactating women in clinical research.[iv]

We believe that by incorporating the unique needs of pregnant and lactating women into the development of an improved clinical trials infrastructure, OSTP can guarantee that pregnant and lactating women are protected from health threats in a future pandemic or other health emergency. We look forward to working with you on this important issue going forward.

Sincerely,

Kathy Castor
Member of Congress

Elizabeth Warren
United States Senator

Brian Fitzpatrick
Member of Congress

Lois Frankel
Member of Congress

Robin L. Kelly
United States Senator

Lauren Underwood
Member of Congress

[i] Kons K, Wood M, Peck L, et al. Exclusion of Reproductive-aged Women in COVID-19 Vaccination and Clinical Trials. *Women's Health Issues*. June 14, 2022. Available at https://doi.org/10.1016/j.whi.2022.06.004.
[ii] Ibid.
[iii] Cray K. A High-Risk Group With a Tragically Low Vaccination Rate. *The Atlantic*. October 22, 2021. Available at https://www.theatlantic.com/family/archive/2021/10/pregnant-people-low-vaccination-rate-covid-19/620458/.
[iv] The 2018 Report to the Secretary of Health and Human Services and Congress of the Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC) and the 2020 PRGLAC Report Implementation plan can be found at https://www.nichd.nih.gov/about/advisory/PRGLAC.

Request for Information; Clinical Research Infrastructure and Emergency Clinical Trials

Federal Register: Request for Information; Clinical Research Infrastructure and Emergency Clinical Trials

Thank you for allowing the Keyrus Life Science USA (KLS) to respond to this RFI, 87 FR 64821. We are very excited to be a part of this RFI and thank you in advance for the opportunity to partner together.

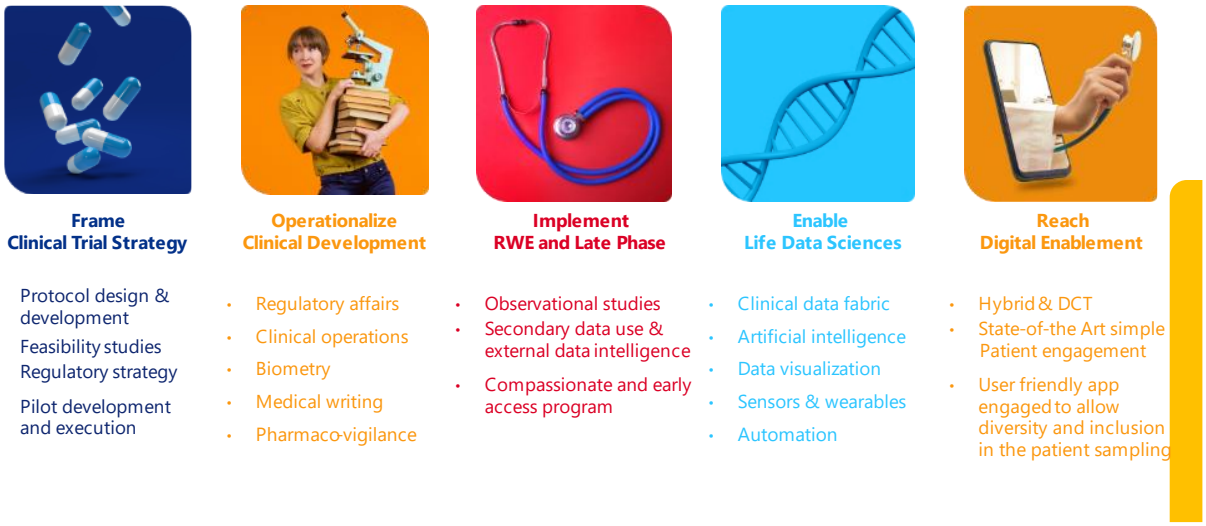
I would like to begin by introducing myself to your team. My name is Karen Marie Josey and I am the Senior Director, Business Development at KLS. I will be your main contact moving forward. I have 30+ years in the commercial and clinical pharmaceutical world. As we look at the exciting possibility of partnering together with OSTP, AP3, ONC and NSC to establish a U.S. level governance structure and outreach to a wide range of institutions, clinical trial networks, and other potential trial sites that can participate in emergency research, both domestically and internationally, I will use my industry experience, contacts and connections to bring the most innovative and effective solutions to you and your teams. I will be joined by members of the KLS clinical trial team, in the establishment of a U.S. level governance structure and outreach to a wide range of institutions, clinical trial networks, and other potential trial sites that can participate in emergency research, both domestically and internationally. We will also to support the expansion of clinical research into underserved communities, and increase diversity among both trial participants and clinical trial investigators. We will design and execute the building of U.S. capacity to carry out emergency clinical trials will enlarge and strengthen the U.S. clinical trials infrastructure overall, by using our 30+ years of clinical trials experience and our multi-centered, multi-partner clinical trial site networks which are already established and contracted.

Keyrus Life Science is a globally connected CRO bringing life data sciences and digital enablement together to fully leverage the clinical research ecosystem and real-world evidence in healthcare, making clinical research activities more reliable, innovative and agile. We provide a full suite of clinical trial services to optimize patient recruitment and engagement, to leverage insights from data, and to unlock new horizons for personalized therapeutic approaches. At Keyrus we have a knack for ethical innovation. The Keyrus Innovation Factory is our innovation incubator that operates on an international scale. We iterate on the latest use cases and technological trends with a spirit of respect, fairness, and progress. Empowering clinical research with data to answers biggest health challenges. Data is the key driver of innovation and the foundation for solutions that enable care improvement and augment clinical research capabilities. We use our connected data approach to promote faster translation of R&D efforts to patients, to improve personalized, predictive, preventive and participative approaches to health concerns.

With more than 30+ years of experience, Keyrus makes clinical trial efficiency and data matter to address the biggest clinical challenges in a positive way to enable long-term success. The graph below is a sampling of the support and management Keyrus can provide to OSTP and all agencies, sponsors, sites and patients involved and effected by an emergency clinical trial.

Keyrus Life Sciences

Unique Positioning to Support OSTP Data Collection for Emergency Clinical Trials and Interoperability Pilot



Like OSTP and all the U.S. affiliated agencies focused on clinical trial emergency readiness, at Keyrus we not only believe it is the data itself that matters, but the problems we can solve by leveraging it. By “making data matter,” we don’t exclusively mean in a clinical trial performance context; we make your data matter from a broader, human-oriented perspective that enables positive change on a larger scale. The kind of broad scale perspective needed in the event of an emergency healthcare crisis in this country.

At Keyrus, we plan to use our scientific and technical expertise to empower OSTP with actionable data-driven insights. Beyond simply understanding data, we use it as a driving force for progress and innovation - a means to a better and healthier future. As data plays an ever-expanding role in all of our lives and across clinical research our experienced team can be there to help OSTP design the interoperability pilot, execute it and analyze the results after the conclusion of the pilot. To us, data is a window into our world, its workings, and the way humans interact with and shape it. Data is the story of our past and the script for our future, making it inherently human. This approach allows our clients to put more focus on the individuals they serve. More broadly, it enables them to use data in a way that will positively shape the future. This is why we focus on extracting insights and value from data - we know it has the ability to move us forward in a positive direction, not just economically, but environmentally, socially and across the most pressing health-related challenges.

If given the opportunity, we would approach your building of a clinical research infrastructure and emergency clinical trial governance, EMA and warm base research with both a present and future-oriented. We would implement solutions that we know from experience do work and that would solve current OSTP challenges, adding immediate value while looking ahead at future opportunities for innovation and progress, with a focus on emergency conditions.

This would enable OSTP to proactively reinvent your clinical trial strategies, to the final benefit of the patients and the country while working in a timely manner. We believe data is the raw material that OSTP will need in order to stay ahead of current and future health crisis occurrences. We are experts at tackling complex problems and providing our public health clients with straightforward, effective and scalable solutions.

Keyrus has always had a focus on diversity and inclusion. We believe a better future begins when we bring the best together. This means a constant emphasis on diversity and inclusion in and outside of the workplace, and persistent dedication to continuing to learn and improve which we would bring to OSTP and all related agencies we would partner with during Emergency Clinical Trials and/or the Interoperability Pilot. Putting our beliefs into action, Keyrus has made a point to develop a strong not for profit (NFP) data practice, providing steeply discounted services to help modernize NFP's infrastructure and reporting capabilities. This enables NFPs to direct grant/donor money to the impact of their mission to provide services to underserved communities.

Keyrus has worked with other governmental agencies that were preparing their systems in the event of emergencies, in these situations, it is critical that these systems are regularly tested and go through real-world simulations to ensure operability in a true emergency scenario. The solution itself needs to provide flexibility for quick configuration changes because these types of emergency scenarios without fail will provide variables unaccounted for. Out-of-the-box solutions typically will be quicker to stand-up but will break much easier when they encounter unexpected behavior or functionality that was not planned for.

One of the other main features of our solution is that we would be providing a completely codified platform that follows best practices in regard to development operations (DevOps). The benefit of leveraging these techniques is that the entirety of the platform (infrastructure, software, and configuration) can be activated programmatically removing human error and vastly increasing the speed and reliability of spinning up the platform when needed. We are happy to give you a capabilities presentation and demo of this technology so you can see the benefits for the program and solution you are building for emergency readiness.

Below you will find the Keyrus solution responses to areas of need for OSTP and related agencies for Clinical Research Infrastructure and Emergency Clinical Trials readiness. We would be very happy to engage in a meeting where our connected CRO team can expand on our ability to support the OSTP team and be 'ready together' for any health crisis that may arise.

1. Governance for emergency clinical trials response

Keyrus Life Science makes it a standard practice to implement governance structures with all our partner across the globe to ensure that our clinical trials and projects are on time, adhering to all study protocols & agency direction and are producing the results, data and analysis needed to be able to make a difference for all patients in the study and all patients in the future. Along

with our weekly and monthly meetings set up with sites, PIs, site staff, for monitoring and clinical trial effectiveness we schedule the governance with a red, yellow, green light approach and ensure all represented parties are present at the face to face quarterly governance meetings as well as weekly and monthly update emails. KLS would utilize this same successful governance execution for the OSTP and related agencies for the emergency clinical trials governance structure. We would develop and action the terms of an Emergency Master Agreement to accelerate response, and identifying a network of available sites based on our current site group (over 20 sites groups, with multiple sites per group, across many therapeutic, rare disease and speciality areas). Since we already have these working relationships and in place, as well as contracts executed, the 'ramp up' to get sites ready and running would be a matter of weeks, meaning that an emergency clinical trial would start up as many as 2 months sooner.

We have 30+ years of experience running global trials, especially and most recently the COVID related trial KLS managed and we have learned the optimal ways to manage interactions with domestic and international regulatory bodies. During a trial we conducted for a Canadian pharma company, we went thru a Health Canada audit. It was the first virtual audit for both KLS and Health Canada. Keyrus emerged from the audit with no comments, notes or criticism. Health Canada praised us for our management, due diligence and flexibility. Those audit results were used for COVID related trials actions in other countries as well. We are submitting a map of our global agency affiliations under sperate cover.

We are very proficient at working across countries, agencies and with multiple partners and stakeholders. Conducting efficiently a worldwide phase 2 clinical study with multiple partners (keyruslifescience.com)

2. Identifying and Incentivizing Research Institutions and Networks; Building Diversity and Equity

Keyrus Life Science, is a connected global CRO with 30+ years of Phase I-IV clinical trial experience. We work with clients from the beginning discovery stages all the way through approval and multi-indication approval. KLS and our subject matter experts have vast experience in overseeing the development of all clinical trial protocols, qualifying our large network of clinical trials sites, training and ready preparing those sites and staff and monitoring the sites and staff throughout the entire clinical trial study process.
We have contracts in place with over 20 large site network groups in North America and can identify, train and engage those site groups within 3-6 weeks. We continue the education and evaluation process during the clinical trial and have a state-of-the-art technology platform that can oversee and evaluated the site staffs understanding, ability and readiness as it relates to the OSTP protocol.

Our site 'Ready' approach is a more effective and efficient way to accelerate enrollment and minimize risks. It helps prevent issues downstream by delivering better training that predicts and improves site and study team performance. This innovative technology streamlines site initiation and reveals which teams and sites are best prepared to successfully conduct a study. In the event of an emergency healthcare crisis in the U.S., both time and preparedness will be key factors. KLS has criteria for establishing for targeting the number and location of sites needed to support clinical trials in case of emergency. We also rely on our SMEs and global readiness team with their 30+ years of site and PI connectivity to help with final recommendations. We employ "quality by design" principles, for designing trials and turn to our clinical data team Keyrus USA so that we capture the data needed without unnecessary complexity that can complicate execution.

We employ a behavioral science-based approach that enhances role specific training and improves performance. When you combine our massive and ready site network, with the quality control 'ready' approach, OSTP can confidently move forward with an emergency clinical trial initiative knowing that KLS will manage the site setup and training in an effective, efficient, and timely manner. In past clinical trials when KLS employed this next generation system, study participants had >90% compliance. This Compelling onboarding engaged participants to continue in the study with only a 1% attrition rate. High engagement, low attrition and faster data capture will improve quality of results and drive new insights for OSTP, most especially when an emergency health care crisis arises, means the difference between getting you need to save lives. Keyrus is committed to bringing OSTP the most innovative technology and tools to design, execute and analyse clinical trials, in a timely manner from Study start up thru trial, completion and drug approval. In past clinical trials when KLS employed this next generation system, study participants had >90% compliance. This Compelling onboarding engaged participants to continue in the study with only a 1% attrition rate. High engagement, low attrition and faster data capture will improve quality of results and drive new insights for OSTP, most especially when an emergency health care crisis arises, means the difference between getting you need to save lives. Keyrus is committed to bringing OSTP the most innovative technology and tools to design, execute and analyse clinical trials, in a timely manner from study start up thru trial, completion and drug approval.

In all use-cases that require a disparate group of users for the collection and analysis of data, there needs to be data structures and formats that all parties adhere to. This is precisely what our FHIR framework accomplishes to make the sharing and accessing of data possible across different sites, user groups, and electronic health records. We routinely expedite data collection through and to clinicals, sponsors, sites and agencies. We do this within the constraints of the clinician workflow. Working with OSTP, the sites, the sponsors, and our Keyrus team we would have a dedicated team in place to monitor all eCRF content to make sure it is collected in real-time accessible to all parties.

The KLS eCRF system provide a flexible software that enables easy study set-up and management. Customers and end users value the simplicity of customizable workflows.

According to our clients, one of the key advantages of using our system compared to other EDC tools, is its quick implementation. A study set-up is possible in weeks not months.

The KLS eConsent software simplifies the consent process, raises patient comprehension and retention, eases workloads for study teams and sites. Flexible and powerful design features allow for the creation of sophisticated and intuitive electronic informed consent forms (eICF) with videos, graphics, and downloadable PDF. The necessary data (both structured and unstructured) will flow securely downstream from the eConsent software into the central data platform.

Informed consents and/or authorizations would be stored in their own document store within the data lake layer (S3). The data regarding that document (patient) will be passed along and used as authorization as we pass data further along into the more centralized layers. The ability to integrate the data from this layer with downstream rules ensure that no patient records without completed consent forms gets centralized together. a front-end technology to create visual representations of the data to provide results across patients and sites will be needed.

Because of our vast site group partnerships and established contracts and our one-stop eConsent platform that can be used and viewed by patients, sites, staff, sponsors and OSTP in real-time, we know from experience that this approach is the best ways to increase the likelihood that users will actually provide the input needed for efficient and effective data capture. Keyrus is very excited to be able to bring our teams together to demonstrate this next generation technology cloud-based ePRO/eCOA platform, APIs and workflow integrations support which we have used to deliver large-scale clinical trials across the globe. Integrating with other clinical trial technology and services, we can bring the high rates of data capture compliance and participant retention we have seen with other partners to OSTP for your current and future project.

It is predicted in the next two years that 40% of clinical trials will be decentralized and pharma and supporting organizations will have to scale their digital trial programs in order to accelerate development timelines and to prevent further trial costs increases. KLS has been employing a DCT approach long before COVID and the need to ‘have to’ to conduct clinical trials that way. For 15+ years, across the globe, we have been bringing the trial directly to the patient. That could mean at their home, work, school or anywhere they live. This means a better chance to reach more patients and thus enrollment, recruitment and retention will all be maximized. This DCT approach always allows for diversity and inclusion especially in the underserviced community because the patients don’t have to travel to the trial site. Over 80% of our contracted clinical trial site partners have engaged in DCT trials with KLS while they remain the lead in all SAEs reporting and clinical trial protocol execution.

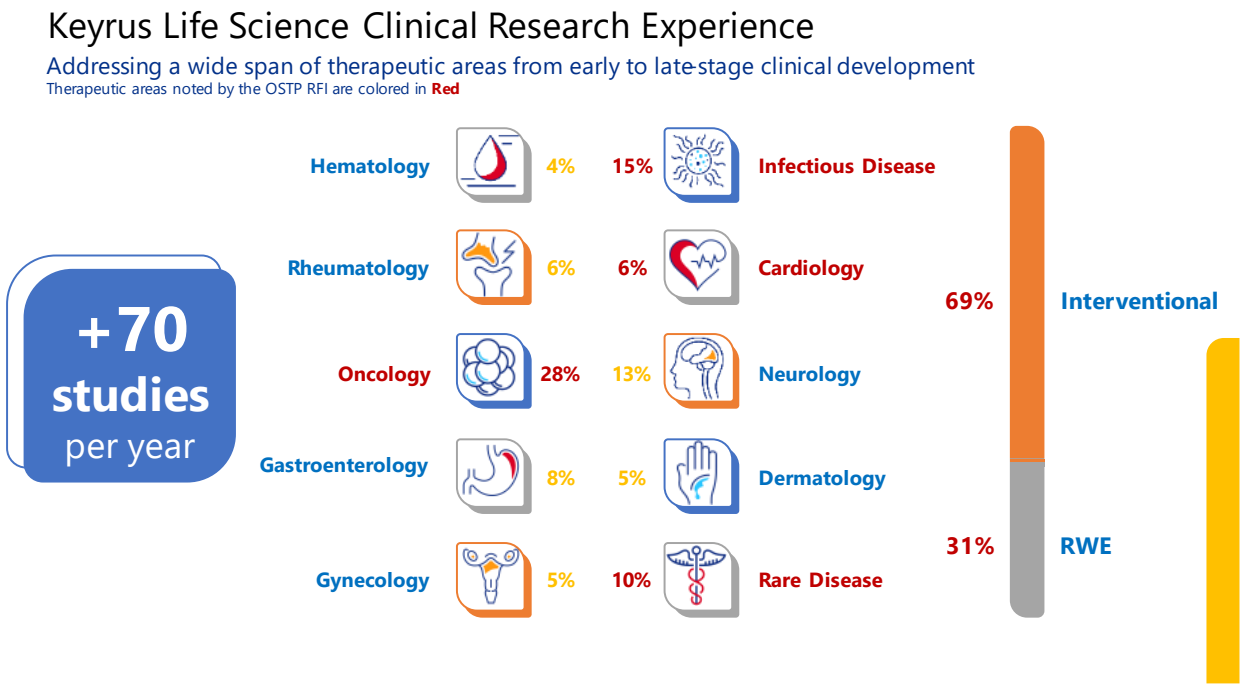
Keyrus has always had a focus on diversity and inclusion. We believe a better future begins when we bring the best together. This means a constant emphasis on diversity and inclusion in and outside of the workplace, and persistent dedication to continuing to learn and improve which we would bring to OSTP and all related agencies we would partner with during Emergency

Clinical Trials and/or the Interoperability Pilot. Putting our beliefs into action, Keyrus has made a point to develop a strong not for profit (NFP) data practice, providing steeply discounted services to help modernize NFP's infrastructure and reporting capabilities. This enables NFPs to direct grant/donor money to the impact of their mission to provide services to underserved communities.

Our KLS clinical trial team and our Keyrus USA data specialists will help OSTP support the expansion of clinical research into underserved communities, and increase diversity among both trial participants and clinical trial investigators.

3. "Warm Base" Research

KLS, in advance of an outbreak or other emergency, will have multi networks and site groups ready to begin carrying out clinical trials to create a "warm base" of clinical research capacity. We have experience from our COVID trial projects in warm base research to be able to gather data under a particular clinical research protocol, but also serve the function of keeping trial sites in a state of readiness to undertake additional or future research. The majority of our warm base study is in the therapeutic focus of infectious diseases. However, across our therapeutic area expertise we have move from contract sign, to study kick off meeting to study start in under 40 weeks. Our expertise in the therapeutic areas of interest for OSTP; infectious disease, cardiology, oncology and rare disease are highlighted in the graphic below.



KLS has several warm base research projects that illustrate our ability to not only gather data under a particular clinical research protocol, but also serve the function of keeping trial sites in a state of readiness to undertake additional or future research. The largest and most recent can

be found outlined on our website https://keyruslifescience.com/en/en/playbook/medical-writing-success-story Keyrus is happy to provide references and project details to the OTSP team if needed.

4. Emergency Master Agreement

Keyrus Life Science has everything in place to execute an emergency master agreement (EMA) with OSTP and related agencies. Because of our dedicated team and nimble staff size we can quickly and efficiently execute an EMA that will allow our teams to begin the clinical trials as soon as possible. KLS would create an EMA with basic terms could be relevant for any coordinated or large-scale emergency clinical trial, such as provisions that allow data gathered under common protocols from a range of sites to be collected, coordination with all sites, data lake information made readily accessible between OSTP, sites, PIs, and sponsors beyond the institutions where the trial was conducted. KLS would use the governance pillars to act as the framework for the EMA. KLS would assure central management of biospecimens, our data teams' expertise to create and monitor a single real-time data platform with single user login for all users, as well as the use of a single Institutional Review Board (IRB). We want OSTP and related agencies to feel confident that Keyrus has experience in these drafting and executing trial master agreements across the globe as described in section 1 of this RFI.

5. Identifying viable technical strategies for data capture; gathering information about a potential data capture pilot

Thank you for the opportunity to share our innovative clinical trial experience and technology solutions in clinical trial readiness as it relates to the OSTP need for a Clinical Research Infrastructure and Emergency Clinical Trials. We are ready to support the efforts of OSTP and related agencies so that a comprehensive and real-time plan for execution is ready if and when it may be needed. We are excited about the opportunity to meet with your team to further discuss the capabilities of Keyrus Life Science and our potential partnership for the future.

For further discussions please contact:

Karen Marie Josey
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Senior Director, Business Development
810-610-4806

www.keyruslifescience.com

eMed®

Response to:

The White House Office of Science and Technology Policy
in partnership with
The National Security Council

Request for Information;
Clinical Research Infrastructure and Emergency Clinical Trials

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Responses

Domestic Clinical Trial infrastructure has been lacking through this pandemic. Time and again, the data that has been most useful for pandemic decision making around vaccines and therapeutics and diagnostics has flowed into the US from overseas. The critical need for new infrastructure that maintains highly scalable, efficient and deployable clinical trials and evaluations that can be stood up in days, not months cannot be overstated. The US needs an "Operation Pilot Light" for trials that will ensure that the infrastructure required for emergency trials and research is ready and available in emergency situations and crises.

Operation Pilot Light (as we might call it for the sake of this particular response) would consist of collaborative infrastructure between government, industry, and academia to ensure trials, population research platforms and data gathering are at the ready, while consuming minimal resources during "peacetime." Operation Pilot Light might in the best of scenarios be an efficient engine that is constantly passively collecting certain biological data that would double both to flag when emergencies may be occurring and also work to drive the data that will inform the trials and research needed.

1) Governance for emergency clinical trials response.

1a) As has been the case with COVID-19, the leadership and governance required to make appropriate decisions in trials will require specialized expertise.

During peacetime, the US should develop a governance strategy that hinges on a national reserve of scientists and leaders from across government, industry and academia who are willing and ready to be "deployed" anytime during a 1-5 year period of time. The scientists and leaders would be prompted to volunteer for the reserve post, and would linked to their specific skillsets and attributes. The National Security Counsel would house a database of such individuals and, along with pre-specified types of trials and research programs that will need to be deployed during specific already-defined types of crises (respiratory virus pandemic, polio outbreak, biological threat, etc…) these individuals would be called to action based upon a more algorithmic assessment of the skills and attributes required for the crisis type. The hierarchy of how these individuals will interact and "show up" to govern the unique response will have already been largely pre-defined before any emergency is upon us - through the development of an emergency playbook that becomes the reference. This will enable fast clarity and objective decision making around leadership and governance and should remove political biases surrounding biological and other apolitical threats.

1e) For threats of the nature and scale that COVID-19 has posed, the institutions that would normally undertake clinical trials and population research largely are unable to move fast enough. Nevertheless, the academic institutions of the United States comprise much of the

specialized expertise of our nation. Therefore, institutional pairings should be identified and put in place early, before they are needed, between industry partners and academic institutions that, combined, can carry out large scale swift trials while breaking down barriers that cost precious time and often lives.

As an example, companies like eMed exist now that have platforms that enable massive scaling of logistics, recruitment and complex procedures to be performed at home for a very wide range of trials. To ensure that trials can be set up quickly, eMed maintains Master Service Agreements and BAA's with academic institutions like Scripps Research Translational Institute and UMass Chan Medical School to spin up new research endeavors fast. Having these MSA's and BAA's has enabled large scale longitudinal studies to move forward for the national Home Test to Treat Program (NIH/ASPR) and the Paxlovid Rebound Cohort Study (NIH/NIAID) on eMed's platform.

Most institutions will always require some sort of individualized contract. Providing incentive for institutions to set up BAAs and MTAs ahead of time, for example through participation in an Emergency Clinical Trials Response Network will make the process of identifying institutions fast and easy. The Emergency Clinical Trials Response Network will be set up ahead of time. Industry will be paired with academic institutions with multi-institutional contracts and MSAs these will additionally carry contracts with government funding agencies. Although initial set up and contracting might be a bit grueling for certain entities given that there may not be a particular emergency to respond to, the incentive will be participation in the network - which might include twice a year meetings by leadership and government, and most importantly being fast tracked into government funded programs when the need for a large and fast trial arises. The network will have a governance set up that would be overseen by the NSC or other US Government agency, with defined roles and responsibilities.

Having these networks formalized through MSAs and BAAs ahead of time will massively improve data sharing across the institutions and will enable clinical trials to capture the exertise of academia and the scale, innovation and speed of industry.

1f) Long delays during emergencies often result from overburdened staff responsible for contracting and responsible for approving research programs and agreements. As a part of the contracting discussed above, each network should include one or more institutional review boards that can work in parallel for different efforts, should they be needed.

Although there are nearly limitless numbers and types of emergencies that may happen, there are basic themes and types of emergency scenarios and limited numbers of types of trials that may need to take place. In setting up the Emergency Clinical Trials Response Network, a major component will be to develop a task force to build future looking protocols across a range of

different scenarios. These protocols can be built, reviewed and discussed by experts and preliminarily reviewed by institutional review boards and other ethics committees within HHS, CDC, FDA, and other health agencies. The purpose will be to have a book of protocols, each with preliminary approvals, that match an emergency scenarios playbook. Upon an emergency and need for rapid scale up of clinical trials (diagnostics, vaccines, therapeutics) the appropriate IRBs will be adopted and adapted appropriately in hours or days, not weeks. Along with the network, institutions will exist and will already be linked to the scenarios playbook for deployment.

The purpose of this approach is to treat clinical trials in a highly regimented and efficient manner, where, like in the military, individuals have their posts, the rules are set and all are ready to be deployed if and when necessary. Operation Pilot Light (discussed above) can and should exist and show that even natural biological threats can be dealt with with the rigor and speed that the US is capable of dealing with foreign enemies.

2) Identifying and incentivizing research institutions and networks; building diversity and equity.

2a) The COVID-19 pandemic has caused an enormous rise in the number of researchers interested in human subjects research and clinical trials. Some of these institutions have developed robust platforms that can scale to hundreds of thousands or millions of participants daily - often through robust logistics, software and recruitment strategies that reach people in their homes.

Many of these institutions, like eMed, will be highly interested to continue to serve the country through continuing to carry out government funded research and trials. During an emergency however, there is a clamoring with little ability to properly assess institutions abilities and understand their strengths and weaknesses.

During peacetime, an “Operation Pilot Light” effort geared towards building and maintaining robust clinical trials infrastructure through the development of a deployable Emergency Clincial Trials Response Network would be critical to identifying approach institutions to carry out the traisl. This effort could initiate well before an emergency, with a steering committee of invited experts tasked to identify through an RFI-like process the institutions that have platforms built to engage in large scale clinical trials research. Development of certain metrics will streamline the process. Features that would make trials deployable to large swaths of the country or globe, fully HIPAA compliant databases and procedures, software platforms that are already built and agile will be critical to evaluate for.

As a part of the process, the government can make available some moderate funding to push institutions to demonstrate proof of principle ability to respond through a series of tasks. These would ensure that the appropriate industry leaders make the cut. Additionally, during peacetime, routine “fire drills” should be conducted that push partnerships and institutions to respond. Relatively little funding will have to be supplied by the federal government to enable companies to undertake these tasks, but the benefits of maintaining the agility, confidence and expertise to deploy fast trials will be well worth it.

2i) Decentralized trials are a massively beneficial approach to greatly scaling trial speed and scope - potentially exponentially. However, a limitation of decentralized trials is often a lack of oversight outside of a brick and mortar location of the use of diagnostics, taking of medications or vaccines. The benefit is the reach and demographics that are enabled through DCTs.

EMed has developed a robust and extremely scalable approach that provides the needed oversight without compromising on reaching all segments of the population, including those who are most rural, poor, or vulnerable. Telehealth Proctoring that can be performed on the order of 100,000’s or millions of virtual visits per day can enable even highly complex trials to be done entirely from home. Emed, for example, has developed a powerful logistics platform that recruits individuals from across all 50 states and internationally, kits and ships out clinical trials kits overnight, to anywhere in the world and provides on-demand instruction using an army of telehealth proctors who are trained at very specific tasks required of a trial. The telehealth proctors can be scaled from maintaining a base of 10’s or 100’s to 1000’s of proctors within a week - each trained appropriately (often over a 40 hour training session) for the task that they will proctor. Software logistics enables appropriate triaging to each proctor for their specified skillset. During the peak of the pandemic, eMed scaled from performing 1-5 thousand sessions per day to nearly 100,000 fully telehealth proctored sessions per day, in just over a week. These types of scaling from “pilot light” to “huge” is not possible without distributing the efforts through decentralized digital trials. Coupling the proctoring with logistics and video and audio data capture and follow-up maintains integrity of the data and enables evaluators of the trials to have confidence that the diagnostics, vaccine or therapy under investigation has been appropriately used and the data represents what actually happened, despite the complete lack of brick and mortar facilities.

Many companies that will be interested to carry out the trials with academic partners additionally already link in to the major national pharmacies for various reasons. This can enable participants who require a vaccine or other biologic that may not be easily administered at home, for instance, to show up at a national pharmacy chain, receive a vaccine under investigation and enroll as a participant in the trial digitally, from a phone or computer for telehealth proctoring and further specimen collections from home. Additionally, in a decentralized framework, the

vaccine could be delivered in person at home and all of the follow up and specimen collections, including blood draws could be done at home.

Currently, eMed is leveraging its telehealth proctoring solution to drive two very large research studies. The first is a nation wide Paxlovid Rebound Cohort Study that monitors individuals for rebound through telehealth proctoring and guides people through a complex series of research activities, at home, including self blood collection using Tasso devices and swabbing, packaging up the kits and shipping back for immunological and virological testing. In the Paxlovid Rebound Cohort Study, the entire recruitment and participation process is remote, despite highly complex asks of participants who often have little to no scientific knowledge. The other large research program is the “Home Test to Treat Program” driven by the Biden Adminstration in which eMed is working with UMass Chan Medical School to evaluate telemedicine across America. Every participant receives kits, developed and shipped by eMed Logistics and uses telehealth proctoring platform to undergo observed testing, get symptomatic evaluations and be directed into telemedicine when needed, with treatment delivery to home and symptom follow up. These types of platforms can scale to much greater numbers and enable decentralized clinical trials to be set up, nationwide, in days or weeks.

All of the data in these efforts should and are shared back with the government (NIH/RADx, NIAID and ASPR) as well as academic partners for evaluation.

These extremely scalable platforms can be sustained with minimal resources through an Operation Pilot Light program or through additional warm base efforts.

ACRO
ASSOCIATION OF CLINICAL RESEARCH ORGANIZATIONS

January 27, 2023

Grail Sipes
Office of Science and Technology Policy
Executive Office of the President
Eisenhower Executive Office Building
1650 Pennsylvania Avenue
Washington, DC 20504

RE: ACRO response to Office of Science and Technology Policy (OSTP) Request for Information: *Clinical Research Infrastructure and Emergency Clinical Trials*

The Association of Clinical Research Organizations (ACRO) represents the world's leading clinical research and technology organizations. Our member companies provide a wide range of specialized services across the entire spectrum of development for new drugs, biologics, and medical devices, from pre-clinical, proof of concept, and first-in-man studies, through post-approval and pharmacovigilance research. ACRO member companies manage or otherwise support a majority of all FDA-regulated clinical investigations worldwide. With employees engaged in research activities in 114 countries, the member companies of ACRO advance clinical outsourcing to improve the quality, efficiency, security, and safety of biomedical research.

ACRO thanks OSTP for releasing this important RFI on *Clinical Research Infrastructure and Emergency Clinical Trials*. ACRO is pleased to provide the following feedback.

Recommendations

In the early stages of the COVID pandemic, the United Kingdom established a scientific committee, the Scientific Advisory Group for Emergencies (SAGE) to provide scientific and technical advice to support government decision makers during emergencies. Taking a capacity management approach, this group prioritized scientific review to determine which trials had the best chance to be productive, which in turn sped up the clinical trial process. We could mirror this effort in the United States. In addition, the development and use of a platform trial protocol specifically to accommodate multiple vaccines directed at the same target would be a much more efficient use of patients and resources. Utilizing a similar approach to the I-SPY trials would enable efficiencies in time, cost, and resources.

The need for an expert group to review emergency clinical trial protocols was illustrated by an April 2021 article in *Nature*[1] by Janet Woodcock and Kevin Bugin of the Food and Drug Administration (FDA). Their analysis suggested that an overwhelming majority of COVID treatment trials—as much as 95 percent—were designed and executed in such a way that not enough patients were enrolled and thus the trials were not statistically

[1] Janet Woodcock and Kevin Bugin, *Trends in COVID-19 therapeutic clinical trials*

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powerful enough to produce meaningful results. To prevent the “wasting” of trials and trial participants, ACRO strongly believes that a high-level scientific committee, with rapid decision-making capability, charged with rationalizing an emergency research portfolio and avoiding an abundance of under-powered clinical trials, should be established. The utilization of platform protocols should also be governed by this committee. This scientific and technical committee to a US emergency response should be composed of experts from government, academia, public health organizations, and industry (inclusive of pharma, technology, and clinical research organizations) in roughly equal numbers.

An approach that could greatly help trial enrollment would be to utilize data analysis across geographies and therapeutic areas and to develop a national database or a collection of databases of potential trial participants. Sponsors and clinical research organizations (CROs) have access to a number of datasets for which appropriate use arrangements could be established. The Centers for Medicare & Medicaid Services (CMS) holds a significant amount of health data that could be leveraged towards this effort as well, as do private health insurers. With guardrails required by HIPAA in place, and a commitment across the health system to offering individuals opt-in opportunities to consent to the use of their data for research purposes, while securing such data from unauthorized access or disclosure, development of national databases or collaborative arrangements for use of a collection of databases of both identifiable and de-identified data for research use is entirely possible.

Similarly, data bank models, such as the UK Bio Bank can make real time review of data accessible to investigators under an agreed-upon governance structure, providing an ability to amend ongoing studies, and increasing the likelihood of success.

Many of the questions in the RFI address research networks. It is ACRO’s recommendation that the US lean heavily on existing sites and networks during an emergency. By existing sites and networks, we are referring to both those created or funded by NIH and the many private-sector research sites that supplement industry trials. A robust infrastructure of sites currently exists, and the government should coordinate with and include them in capacity planning and fund programs that address research gaps in historically underrepresented communities. Networks cobbled together during a crisis are unlikely to be successful and therefore time should be spent, before the next inevitable emergency, shoring up existing networks—whether federally funded or private—and investing in new ones where needed.

The use of already existing networks is particularly important when considering pediatric patients and other vulnerable and displaced populations. As we have seen throughout the COVID-19 pandemic, these populations are most adversely affected. Therefore, existing networks already “at the ready” would help to best deliver trial interventions.

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Consistent with NIH policy and FDA recommendations, any sites/networks that do not agree to the use of a single IRB should be ineligible for funding or selection in the event of an emergency. Any networks participating should be required to use protocol templates, emergency master agreements, and encouraged to use remote technologies and services to grow their capacity. Additionally, the traditional concept of the research site as a clinic- or hospital-based physical entity, should be enlarged to include the use of home-based and/or other remote study locations to facilitate patient recruitment, retention, and diversity, all of which are acutely impacted during biomedical emergencies. Decentralized trial activities and elements, which the FDA widely embraced during the COVID pandemic, should be extensively applied to advance trial conduct in future emergencies.

One hurdle that ACRO members came up against during the COVID-19 pandemic was the availability of laboratory and other medical supplies. Many investigators and research organizations had trouble accessing lab supplies due to the volume of research testing going on across vaccine and treatment trials in addition to clinical diagnostic testing. In several countries CROs and research sites were not included on the lists of organizations given priority access to those supplies, which caused delays throughout a number of trials. Amending such lists in the future to stipulate that investigators and approved research organizations should have access to laboratory and other medical supplies, on the same priority level as clinical diagnostic testing and treatment facilities, would help to mitigate such delays, but only if production capacity is expanded. Equally important is the need to maintain and expand “warm base” manufacturing capabilities for supplies and equipment that are likely to be needed by both clinical testing and treatment facilities and by research facilities during future emergencies and that were in short supply for both types of facilities during the pandemic.

The questions in section 2 of the RFI relate to improving diversity and equity. One way to do this is to review private sector initiatives for new models of embedding research in the US healthcare system and particularly locational that serve underrepresented communities. Industry has been building research structures into communities, so that trials are more accessible and the time/travel burden on patients is lessened. Among these efforts are partnerships with health care clinics—companies with broad reach like CVS and Walgreens—and the provision of home health nurses and the use of telehealth services to support routine safety assessments. Embedding research into healthcare delivery systems, including hospitals, group practices, community clinics, and home health agencies is paramount.

Lastly, we would put forward a policy recommendation that the US consider a national ‘license’ or other recognition for Principal Investigators (PIs) and nurses to preempt state law during the period of a federal public health emergency declaration in order to address problems created by state licensure of healthcare providers that were observed during the COVID pandemic. This emergency national license would be targeted specifically to PIs and nurses engaged in clinical research and not available to

healthcare providers only providing regular clinical care. The Nurse Licensure Compact (NLC) program already in place in the US could be a model. A number of ACRO members have recounted instances during the COVID pandemic where trials were delayed or canceled due to state licensure issues. This proposed solution would be extremely helpful for closing gaps in the use of home health evaluations and interventions as part of an ongoing clinical trial. Note that the issue of cross-state licensure also impacted the delivery of telemedicine across state borders during the pandemic but was significantly remedied by altered reimbursement models.

Conclusion

Thank you for this opportunity to provide feedback on the Clinical Research Infrastructure and Emergency Clinical Trials RFI. If we can provide additional details or answer any further questions, please do not hesitate to contact us.

Respectfully,

Sophia McLeod
Director, Government Relations
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ACRO

AMERICAN SOCIETY OF HEMATOLOGY
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ASH Recommendations to the OSTP and NSC's RFI on Clinical Research Infrastructure and Emergency Clinical Trials

The White House's Office of Science and Technology (OSTP) and National Security Council (NSC) through this request for information (RFI) seek to gather information on how the US government might be able to build the clinical research capacity needed to appropriately respond in the event of an emergency by:

- Identifying processes for developing emergency clinical trial protocols,
- Determining how to capture clinical trial data through consistent data elements reported across participating sites; and
- Identifying efficient ways to carry out clinical research that attracts diversity among trial participants as well as among the investigators who lead clinical trials.

Below are ASH's recommendations in response to OSTP and NSC's request (submitted electronically to emergencyclinicaltrials@ostp.eop.gov).

1) **Governance models/structures for effective emergency clinical trials response**

ASH believes one centralized structure that combines multiple government and federal entities including the Biomedical Advanced Research and Development Authority, National Institutes of Health, Centers for Disease Control and Prevention, the US Food and Drug Administration (FDA), and Veterans Affairs is needed for an effective emergency clinical trials response. A centralized structure, that coordinates and oversees an emergency clinical trial response, and also capitalizes on the relevant expertise (i.e., basic, translational, and clinical research as well as population studies) of each of these government/federal agencies, will be vital to expediting the development, approval, and distribution of therapies that evolve from emergency clinical trials. This centralized structure should include:

(a) the development of clear and streamlined protocols for emergency clinical trials;

(b) information on how academic institutions and pharmaceutical companies could engage with the centralized structure of government/federal entities to facilitate an emergency clinical trials response.

Regarding best practices for designing trials that streamline relevant data capture without unnecessary complexity, ASH believes the model implemented by most COVID response teams could be expanded to any acute problem. This model included the design of adaptive trials with a single international institutional review board (IRB), utilized a single protocol in which treatment arms were eliminated when response was poor, while new arms were added as new agents became available. In addition, patients were recruited using electronic medical records. An example of a COVID trial that implemented this model successfully was outlined in: ATTACC Investigators; ACTIV-4a Investigators; REMAP-CAP Investigators, Lawler PR, Goligher EC, Berger JS, Neal MD et al. Therapeutic anticoagulation with heparin in noncritically ill people with COVID. NEJM 2021;385(9):777-789.

ASH also recommends that for emergency clinical trials, the following trial design principles be implemented:

(a) Development of protocols that clearly include an outline of plans to engage and recruit groups that are predominantly underrepresented in clinical trials. FDA's Diversity Plans to

Improve Enrollment of Participants From Underrepresented Racial and Ethnic Populations in Clinical Trials could be very vital in this regard.

(b) Inclusion of decentralized trial techniques to facilitate access to patients (e.g., telehealth, satellite trial sites in local communities, etc.).

(c) Uniform collection of data related to patient outcomes i.e., incidence of hospitalization, duration of hospitalization, in hospital mortality, overall mortality, and quality of life. In addition, having a central repository where all studies enter their endpoints in a consistent fashion will allow for comparison across agents.

With regards to criteria for establishing a target number and location of sites needed to support clinical trials in case of emergency, ASH recommends that the US government consider the following:

(a) Leveraging the infrastructure of academic institutions especially those that have protocols in place to set up satellite sites in areas predominantly impacted by the disease.

(b) Collaborating with networks of providers, patients, and sites like those developed by the ASH Research Collaborative (ASH RC). The ASH RC brings together data from the nation's largest academic referral centers providing care for patients with underlying blood disorders in sickle cell disease and multiple myeloma. Participating providers, patients, and sites within these networks are research ready and contribute patient-level data from electronic health records and custom case report forms, in addition to other data sources including patient generated health data. The US government's collaboration with organizations like ASH RC, would give it access to a network of clinical trial centers as well as individual providers and patients within these networks through electronic portals. It would also provide the government with an avenue for data access, storage, and tracking.

(c) Partnering with large medical record providers such as EPIC, Cerner, and other vendors to build screening tools that will allow access to the health records of millions of Americans and potentially identify patients who could be suitable candidates for a trial. Alternatively, for subpopulations of immunocompromised patients, existing data platforms such as the ASH RC's Data Hub already aggregate electronic health record data from multiple EHR systems which could be leveraged as a single source.

As for methods of communicating decisions to begin emergency clinical trials, ASH recommends that the US government take advantage of communication channels that professional societies have, to reach investigators and clinicians interested in participating in such trials and/or may already be conducting "warm based" research that could be informative to the US government.

2) Methods to identify and incentivize research institutions and networks to build diversity and equity as part of clinical trial practice

Diversity, Equity & Inclusion (DEI) is a priority for ASH and the Society is committed to supporting scientists and clinicians from all backgrounds, especially those underrepresented in medicine as well as elevating diverse voices across the patient and healthcare communities. Given that a lack of diversity in clinical trials leads to health inequities in medicine, ASH

recommends that the US government require all trial sponsors seeking funding to include a diversity plan that seeks to engage both a diverse patient population and a diverse clinical trial workforce.

Adequate funding support for decentralized trials with a clearly defined DEI plan will encourage trial investigators to recruit diverse patient populations, train a diverse workforce, and support effective tracking of their progress in meeting DEI enrollment goals outlined in the study protocol. Decentralized services such as the use of remote clinical trial coordinators or data extraction directly from the electronic medical record would incentivize participation from clinical trial sites caring for underserved populations.

For effective implementation of emergency clinical trials, existing networks that are engaged in warm based research need to be adequately funded. ASH recommends that the government allocate adequate funding to support the infrastructure needed to effectively run networks of providers, patients, and sites. Very few networks receive their core funding from the federal government, and when a specific disease area is associated with an emergency issue like a pandemic, these networks (that have track records for successful trial launch and completion on a grant-specific basis) are often unable to meet the need, despite the desire of the participating sites and their principal investigators. For example, there are very few pediatric hematology disease-focused networks that receive core funding support from the federal government. Adequate funding of these networks prior to an emergency will equip them to quickly execute on a trial(s) in the case of an emergency.

3) **Hematologic disease areas that are suitable for "Warm Base" research and how this type of research can be implemented effectively**

Primary hematologic disease areas that are suitable for warm base research are those inclusive of patients most at risk from severe consequences of infection, for example immunocompromised patients with hematologic cancers such as multiple myeloma, lymphoma, and leukemia. As a cross-cutting disease area, venous thromboembolism is another hematologic disease that is ideal for warm base research as it crosses all age groups, occurs more frequently in high-risk groups (e.g., patients with cancer, hospitalized patients, underrepresented populations), and the incidence increases in infected patients. Sickle cell disease is another hematologic disease that is suitable for warm base research given that it impacts a predominantly underserved patient population (i.e., African Americans and Hispanics), and can cause spleen damage and other immune system problems that puts the patient at higher risk of infection from certain pathogens.

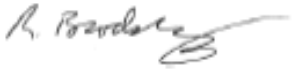
Successful implementation of warm base research in these areas in order to create a basic level of surge capacity for emergency clinical trial research is key. To that end, ASH recommends that in regular times (prior to an emergency), sites and networks conduct warm base research by testing different methods for prospective real world evidence generation, including embedded enhanced data collection, decentralized and pragmatic trials. These methods would be layered atop of routine real world data collection throughout the network. The clinical and scientific objectives of such warm base trials during non-emergency times would be to accelerate research and collaborative clinical practice for underlying diseases. During emergencies, the network's experience with baseline and embedded prospective real world evidence generation could be applied to engaging the network to meet the needs of pandemics or other emergencies.

In the disease areas noted above, warm based research specifically focused on improving clinical risk assessments, identification of biomarkers, understanding of disease pathogenesis, and incorporation of pharmacogenomic data to assess the safety and efficacy of novel therapeutics will generate critical data essential to the design of emergency clinical trials.

4) **Recommendations to inform the development of Emergency Master Agreements that foster the implementation of emergency clinical trials.**
ASH believes existing networks such as the ASH RC could be an efficient way for the US government to negotiate and develop Emergency Master Agreements to be used when emergency clinical trials are needed. The concept of a single IRB, aggregated data collection, data access, and establishment of publication policies are well known to these networks and could serve the US government well during times of emergencies.

ASH thanks the OSTP and NSC for the opportunity to comment on this important subject and looks forward to serving as a resource for the White House on this issue. Please contact ASH's Deputy Director, Scientific Affairs, Alice Kuaban, MS, at akuaban@hematology.org for any additional information.

Sincerely,



Robert Brodsky, MD
ASH President

January 27, 2023

The Honorable Arati Prabhakar
Director
Office of Science and Technology Policy
1650 Pennsylvania Avenue NW
Washington, DC 20502

Re: Request for Information; Clinical Research Infrastructure and Emergency Clinical Trials

Dear Director Prabhakar:

Amazon Web Services, Inc. (AWS) appreciates the opportunity to provide comments on ways to conduct large scale clinical trials to address emerging diseases and during a national emergency. Policies to accelerate the use of decentralized trials—where patients can participate in research remotely and via local healthcare providers—can serve as the foundation to a national approach that would both support preparedness for future public health threats and help find cures for cancer and many chronic conditions that afflict millions of Americans every year. We encourage the Office of Science and Technology Policy (OSTP) to work with federal agencies and the research community to create the underlying technical and governance infrastructure before it is needed in an emergency situation and to support research for non-emergent, chronic, and rare diseases.

Currently, clinical studies—for communicable diseases, chronic conditions, and unmet needs—often require patients to enroll in trials and physically appear at the site administering the research. As a result, many patients are unable to enroll in studies because they are not located near or otherwise unable to access the site leading the trial. For example, more than half of cancer patients don't have a local trial site for their specific cancer.[1] Through decentralized trials, these patients could participate in trials by data collection in their homes or a local site. These barriers to individuals enrolling in clinical trials can also result in a lack of racial and ethnic diversity among participants.[2] Enabling patients to participate remotely can further democratize clinical trial enrollment—reducing disparities in access to novel therapies and enhancing the research available to understand whether new treatments affect subpopulations in different ways. Finally, more than 80% of studies don't meet recruitment timelines.[3] Decentralized trials can accelerate enrollment to reduce delays and bring cures to market faster.

AWS has worked with researchers, life science companies, vendors, and other organizations to support decentralized trials. For example, AWS customer THREAD—which has developed a fully configurable, cloud-based platform for running decentralized trials—estimates that it can support up to 30% time and cost savings and five times more inclusive enrollment versus industry benchmarks.[4] As the COVID-19

[1] American Cancer Society Cancer Action Network. "Barriers to Patient Enrollment in Therapeutic Clinical Trials for Cancer: A Landscape Report." 2018. https://www.fightcancer.org/sites/default/files/National%20Documents/Clinical-Trials-Landscape-Report.pdf.
[2] Blumenthal, David and Cara James. "A Data Infrastructure for Clinical Trial Diversity." *New England Journal of* Medicine. June 23, 2022. https://www.nejm.org/doi/full/10.1056/NEJMp2201433.
[3] Thoelke, Kent. "There's a Silent Crisis in Clinical Research. And it's not Covid-19." *Stat News*. Oct. 28, 2020. https://www.statnews.com/2020/10/28/recruitment-retention-silent-crises-clinical-trials/
[4] "THREAD Scales Decentralized Clinical Trials Across 60 Countries Using AWS." Amazon Web Services. 2022. https://aws.amazon.com/solutions/case-studies/thread-case-study/

pandemic accelerated and the need for remote trials increased, THREAD used cloud services to scale its decentralized trials and electronic clinical outcome assessment to 60 countries.

This example and many others from the COVID-19 pandemic showcase the ability of decentralized trials to modernize the clinical research environment in support of both emergent needs and to combat chronic, rare, and life-threatening conditions.

Government actions needed to support decentralized trials

OSTP, in considering the development of a more advanced system to gather data during an emergency or pandemic, should ensure that the same infrastructure can also support other types of research—including for chronic and rare conditions. To achieve that goal, OSTP should collaborate with the Office of the National Coordinator for Health Information Technology (ONC), Centers for Medicare & Medicaid Services (CMS), National Institutes of Health (NIH), and Food and Drug Administration (FDA) on policies that establish both the governance and technical capabilities ahead of emergency situations. The creation of this governance and technical infrastructure would serve as a "data highway" to enable appropriate, privacy-preserving research.

First, the Administration should include a diverse group of organizations in the establishment of a nationwide research infrastructure. Those relevant organizations include hospitals, healthcare providers, and public health departments to reflect the variability in scenarios where decentralized trials would best support research. For example, some research will focus on patients located in healthcare facilities—and those organizations should have the capabilities needed to share data as part of a decentralized trial model. However, in the event of large-scale communicable diseases, data generation to support studies may be more appropriate in remote settings, including patients' homes or outdoor venues. In these cases, public health departments may lead remote data collection as it would be impractical or unsafe to test, triage, or otherwise collect data in a healthcare facility.

Second, OSTP should work with federal agencies to create mechanisms for organizations to share data on their capabilities (e.g., in-patient capacity), clinical areas of expertise (e.g., infectious disease or cancer), and adoption of advanced data collection and analytic tools. This information will ensure that researchers can identify organizations able to contribute data during an emergency and those facilities that can collaborate on other types of research. OSTP should work with NIH and CMS to appropriately leverage data already submitted for other programs—such as to meet research, grant, or other compliance requirements—for aggregating this data.

Third, the governance created before emergency situations should also include development of data use agreements to apriori address potential hurdles to the sharing of information. These data sharing agreements could indicate the conditions for data sharing, such as during a declared public health emergency or at the direction of the patient. OSTP suggests the creation of an "Emergency Master Agreement" to define and address key terms and topics, such as use of Institutional Review Boards. We agree with OSTP on developing these agreements, and encourage OSTP to consider the use of these kinds of agreements for non-emergent situations, such as to support cancer research. Emerging policies—such as the Trusted Exchange Framework and Common Agreement—could offer a starting point for the data sharing agreement and other governance needs.

Finally, governance should include agreement on data standardization requirements, including definitions and use of common codes and nomenclatures. ONC via its electronic health record certification program, the Interoperability Standards Advisory, and other initiatives can accelerate data

standardization to enable greater alignment among decentralized trial participants. In addition, CMS should use its payment policies—including via new measures in the Promoting Interoperability program—to encourage providers to participate in decentralized trials via the creation of new measures.

Ensure cloud choice by researchers

While we support the creation of governance and technical systems to support more robust research, AWS also cautions against approaches that would require use of specific cloud service providers or other technology. In implementing any policies or infrastructure to accelerate research, the Administration should enable researchers and organizations to select the technology and cloud services that best help them innovate, better understand illnesses, and support biomedical discovery. In allowing researchers to select the cloud services that work best for them, scientists have fewer barriers to use analytic tools on which they rely and other data to more cost-effectively and efficiently advance their scientific understanding and accelerate the time for cures to reach patients.

In implementing a clinical research infrastructure, we encourage the Administration to release guidance that explicitly supports researcher choice in the cloud services they use. We also encourage the Administration to ensure this choice as part of grants and procurements—including with subcontractors—used to support this clinical research infrastructure.

Responses to select OSTP questions

In addition, OSTP requests input on several questions. OSTP requests comments on whether to create a centralized governance model with federal agency membership. Any governance model should also include representatives of those organizations that can support the sharing of relevant data, including healthcare organizations and cloud service providers. In addition, even with a centralized governance process, the developed infrastructure can remain decentralized with appropriate controls and policies to support the use of data to accelerate research in privacy-preserving ways.

OSTP also requests comments on enrollment of vulnerable populations, including pediatric patients. The development of a governance and a technical infrastructure to support decentralized trials would enable the identification of facilities and data to support enrollment of underrepresented communities. Pediatric cancer, for example, represents a promising model. Groups like the Children's Brain Tumor Network are developing and implementing approaches that enable access to information from hospitals around the country to support research to find cures for childhood brain cancers. Similar models can support the secure use of data for other underrepresented communities.

Finally, OSTP seeks input on the establishment of "warm base" research wherein facilities would be in a constant state of readiness in the event an emergency trial is needed. The establishment of governance and technical capabilities to support research for emergent and non-emergent needs (e.g., cancer and chronic conditions) would create this "warm base" to enable both readiness for emergent needs and research into other medical conditions. The development of a decentralized trial network would serve as this "warm base" as facilities would already have national data sharing and research needs built in to their standard operating procedures.

Conclusion

AWS appreciates the Biden Administration's interest in better preparing for future threats by creating the infrastructure needed to support emergency trials before emergencies arise. AWS encourages the Administration to consider creating a decentralized trial capacity that can be used in an emergency and to support the identification of cures for ongoing health risks—including cancer, chronic conditions, and

rare diseases. OSTP should work with federal agencies to establish policies to support this decentralized research capacity, and ensure participation by both traditional healthcare providers and other organizations needed to support research needs.

Sincerely,

Blair Anderson

Director
AWS Public Policy

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January 27, 2023

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Office of Science and Technology Policy
Eisenhower Executive Office Building
1650 Pennsylvania Avenue
Washington, D.C. 20504

RE: Docket No. 2022-23110: Request for Information; Clinical Research Infrastructure and Emergency Clinical Trials

To Whom It May Concern:

The Pharmaceutical Research and Manufacturers of America ("PhRMA") is pleased to submit these comments to the Office of Science and Technology Policy (OSTP) in response to the Notice of Request for Information (RFI) on clinical research infrastructure and emergency clinical trials.[1] PhRMA recognizes OSTP's commitment to advancing an infrastructure that can support clinical trials to address outbreaks of disease and other emergencies, the expansion of clinical research into underserved communities, and increase diversity among both trial participants and clinical trial investigators. PhRMA and its member companies believe that creating a sustainable network of sites in underserved communities will help ensure ongoing access to clinical trials for those who want to participate in both emergency and non-emergency situations, ultimately helping to enhance diversity in clinical research and advance health equity.

PhRMA is a voluntary, nonprofit association that represents the country's leading biopharmaceutical research and biotechnology companies, which are devoted to discovering and developing medicines that enable patients to live longer, healthier, and more productive lives. Since 2000, PhRMA member companies have invested more than $1.1 trillion in the search for new treatments and cures, including $102.3 billion in 2021 alone.

I. GENERAL COMMENTS

We appreciate OSTP's solicitation of feedback on "how to ensure that trial sites in underserved areas are included [in an emergency clinical trial infrastructure] and how to increase diversity both among study participants and among the investigators." PhRMA and its member companies are committed to enhancing diverse participation in clinical trials, including identifying and addressing potential barriers to enrollment, retention, and a positive patient experience.[2] PhRMA applauds the OSTP for convening the public meeting "Preparing U.S.

[1] 87 FR 64821; Notice of Request for Information (RFI) on Clinical Research Infrastructure and Emergency Clinical Trials (October 2022). Available at https://www.govinfo.gov/content/pkg/FR-2022-10-26/pdf/2022-23110.pdf
[2] See comments filed by PhRMA on Aug. 7, 2021, in response to Draft Guidance for Industry - Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs; See comments filed on Jun 29, 2020 in response to Request for Comments – Office of Minority Health and Health Equity Strategic

Clinical Trials Infrastructure for Emergencies: A White House Virtual Roundtable Discussion"[3] on January 12, 2023, and seeking stakeholders' input.

PhRMA shares OSTP's recognition of the importance of having an infrastructure that supports emergency clinical trials and agrees with OSTP that one goal of such an infrastructure should be to "support the expansion of clinical research into underserved communities, and increase diversity among both trial participants and clinical trial investigators."[4] PhRMA believes an important part of any such infrastructure is the need to support participation and access of diverse populations. PhRMA understands that addressing potential barriers to clinical trial enrollment is a key consideration.

As we look at the development of new medicines during both emergency and non-emergency situations, it is essential to take meaningful action to help ensure that underserved and underrepresented communities, who have historically faced barriers to participating in the development of health care advances, are given the opportunity to be included every step of the way. As an emergency infrastructure is contemplated, it will be critical to think through a robust education and outreach effort to address potential misperceptions that "emergency" suggests any jeopardizing of a focus on safety and efficacy.

In addition to the general comments above, PhRMA provides specific comments in response to the RFI below.

II. SPECIFIC COMMENTS

A. Effective Ways to Increase Diversity

1. Expanding Clinical Research Sites in Underserved Areas

Enhancing diversity in clinical trials depends on identifying and reducing barriers to clinical trial access and participation. To this end, there is a need to work with patients, health care providers, and clinical trial investigators to understand barriers and identify approaches to address these barriers and enhance access to clinical trials for diverse patient populations by:

- Taking into account the needs of diverse populations in clinical trial design.
- Adopting enrollment and retention practices that enhance inclusiveness and make trial participation less burdensome for participants.
- Broadening eligibility criteria to increase diversity in enrollment when scientifically and clinically appropriate.

Priorities; See comments filed on Sep. 9, 2020 in response to Request for Comments - Office of Women's Health Strategic Priorities.; See comments filed on June 13, 2022 in response to Draft Guidance for Industry- Diversity Plans to Improve Enrollment for Participants From Underrepresented Racial and Ethnic Populations in Clinical Trials.

[3] https://www.whitehouse.gov/ostp/news-updates/2023/01/06/preparing-u-s-clinical-trials-infrastructure-for-emergencies-a-white-house-virtual-roundtable-discussion/

[4] *See* 87 Fed. Reg. at 64821.

PhRMA believes that building trust in underserved communities and acknowledging past wrongs is an important first step in enhancing clinical trial diversity.[5] Some patients may not trust medical research due to the historic record of mistreatment.[6] Today, patients and research participants' rights are protected by law and ethics committees, including institutional review boards that oversee clinical trials.[7]

PhRMA also believes in the importance of enhancing education about the role of clinical trials throughout the medical community and throughout the range of potential study participants and trusted thought leaders to enhance awareness of and diversity among clinical investigators, clinical trial support staff, and others that can help broaden representation and participation in the clinical trial process. The clinical trial process including the recruitment and retention of patients is complex and multifactorial. The lack of participation by historically understudied populations often is due to lack of clinical trial awareness at hospitals and clinics that treat diverse populations. To address this gap, PhRMA believes that it is important to conduct outreach to the medical professionals in underserved communities and support trial sites with comprehensive education on medical product development. There is a need to support the recruitment and retention of clinical trial personnel with diverse backgrounds, including racial and ethnic backgrounds, and support the collaboration of trusted messengers to educate underserved communities on clinical trials.

Another effective way to increase diversity in study participants is to ensure adequate community outreach by improving clinical trial awareness, community health education and individual health literacy. Educational efforts are a key component of reaching underrepresented populations. Outreach efforts should be aimed at increasing access and reducing barriers for underrepresented and diverse populations to participate in clinical trials. This can be done by partnering with health and community advocacy groups to reach underrepresented populations, to increase clinical trial awareness, and provide access to potential opportunities for participation.

2. *Use of Decentralized Clinical Trials and Technological Innovations Such as Digital Health Technologies*

The conduct of clinical trials may result in recruitment challenges and enrollment barriers that may occur as a result of factors such as site location, planned visit schedules, as well as travel

[5] PhRMA members voluntarily adopted the Clinical Trial Diversity Principles, which aims to increase the participation of underrepresented populations to clinical trials. Principles on Conduct of Clinical Trials & Communication of Clinical Trial Results. Available at https://phrma.org/-/media/Project/PhRMA/PhRMA-Org/PhRMA-Org/PDF/P-R/PhRMAPrinciples-of-Clinical-Trials-FINAL.pdf.

[6] The U.S. Public Health Service Syphilis Study at Tuskegee. Available at https://www.cdc.gov/tuskegee/timeline.htm.

[7] Institutional Review Boards (IRBs) and Protection of Human Subjects in Clinical Trials. Available at https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/institutional-review-boards-irbs-and-protection-human-subjects-clinical-trials

and financial implications. There is a potential for digital health technologies (DHTs) to provide scientific and practical advantages in supporting the assessment of patients by generating information outside of the traditional clinic visit though it must be recognized that significant variability in access to broadband and digital technologies. DHT tools, which encompass a range of solutions that include digital apps, in-home testing, remote monitoring and diagnostics, and other technologies, may help improve diverse participation in clinical trials when coupled with other efforts and resourced appropriately. The use of DHTs can support and enable the conduct of decentralized clinical trials (DCTs), the clinical investigations in which some or all trial-related procedures and data acquisition take place at locations remote from the investigator. DCTs can help improve access for patients by reducing the in-person clinical trial site visits and helping reach patients who may not otherwise be able to easily access a clinical trial.

PhRMA supports the development and use of additional technology tools to support a health emergency clinical research infrastructure. In the specific context of an emergency or large-scale disease outbreak, the use of DHTs and DCTs can provide increased access for patients to clinical trial networks. Throughout the COVID-19 pandemic, DCT and DHT tools were helpful in conducting clinical trials and reaching underserved communities. The Prescription Drug User Fee Act VII and the Food and Drug Omnibus Reform Act[8] will build upon these lessons learned during the COVID-19 pandemic and advance the use of digital technologies, decentralized clinical trials, and other novel clinical trial designs to help increase clinical trial access for patients and enhance clinical trial diversity and enrollment.[9]

B. "Warm Base" Research

PhRMA believes a community-based infrastructure that supports underserved communities is important not just for emergency clinical research, but for overall equitable access to clinical trials. Creating an infrastructure that includes a network of clinical trials sites connected through and supported by robust communication, community relations, ongoing site training and mentoring, sustainable support and standardized platforms and metrics. These are important components of a community-based infrastructure to support clinical trials. Having a network of sites in a state of readiness to undertake additional or future clinical research, i.e., a "warm base," can help facilitate clinical trials more efficiently during an emergency.

Over the past two years, PhRMA has solicited feedback from thousands of stakeholders – patients, providers, clinical trial experts and racial justice experts - to thoroughly understand the systemic challenges to enhancing clinical trial diversity and help build towards actionable advancements.[10]

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[8] *See, e.g.,* Pub. L. No. 117-328, §§ 3605-3603 (directing FDA to "convene a public meeting to discuss the recommendations provided by [FDA] during the COVID-19 emergency period to mitigate disruption of clinical trials" and issue or revise draft guidance on "recommendations to clarify and advance the use of" DCTs)

[9] For more info, see https://www.fda.gov/media/151712/download

[10] The initiative follows more than two years of PhRMA-led stakeholder engagement to assess barriers to clinical trial participation and identify tangible actions and goals that can make a difference. PhRMA Joins Top Academic Leaders to Announce New Community-Based Initiative to Enhance Clinical Trial Diversity. For more info,

III. CONCLUSION

PhRMA and its member companies support efforts to enable emergency clinical research and build capacity to conduct coordinated and large-scale clinical trials across a range of institutions and sites to address outbreaks of disease and other emergencies. PhRMA appreciates the opportunity to provide comments on this RFI and welcomes additional questions regarding this topic.

Respectfully submitted,

/s/

Anne McDonald Pritchett, PhD,
Senior Vice President,
Policy, Research, and Membership
PhRMA

/s/

Maria Apostolaros, JD, PharmD, MS, BSc, RPh, CCEP
Deputy Vice President,
Science and Regulatory Advocacy
PhRMA

https://phrma.org/resource-center/Topics/Access-to-Medicines/PhRMA-Joins-Top-Academic-Leaders-to-Announce-New-Community-Based-Initiative-to-Enhance-Clinical-Trial-Diversity

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January 27, 2023

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Sent electronically to emergencyclinicaltrials@ostp.eop.gov

RE: Clinical Research Infrastructure and Emergency Clinical Trials Request for Information (RFI)

Ms Sipes:

On behalf of McKesson Corporation (McKesson), thank you for the opportunity to provide comments regarding the Request for Information, Clinical Research Infrastructure and Emergency Clinical Trials.

About McKesson
McKesson is a global leader in healthcare supply chain management solutions, retail pharmacy, community oncology and specialty care, and healthcare information solutions. McKesson partners with pharmaceutical manufacturers, providers, pharmacies, governments, and other organizations in healthcare to help provide the right medicines, medical products, and healthcare services to the right patients at the right time, safely and cost-effectively. As a mission-driven company, we are focused on working with our customers and partners to advance health outcomes for *all*.

In the oncology space, McKesson is a leader in advancing cancer clinical research and improving cancer care and patient outcomes. We support The US Oncology Network (The Network), one of the nation's largest and most innovative networks of community-based oncology physicians. Ontada®, our oncology data science and technology business, leverages our unique oncology provider network strength in developing clinical and operational technologies. Generating structured and unstructured oncology data across more than 2,700 oncology providers in 40 states, Ontada focuses on oncology real-world data and evidence (RWD/E), clinical education, patient engagement and best-in-class provider and research technologies.

For more information on how McKesson has led the healthcare industry in the delivery of medicines and healthcare products, including our critical partnership with CDC and ASPR on pandemic relief, we refer you to our website at www.mckesson.com. In sum, our unique 360-degree view of the healthcare system provides us with a distinctive vantage point, and our public-policy platform is driven by the core belief that the ***Patient Comes First***.

Introduction
We applaud OSTP's recognition of the need to advance the nation's clinical research infrastructure and to expand clinical trials into the community and alternative sites of care. The COVID-19 pandemic highlighted the urgency of addressing longstanding regulatory, legal, and

operational barriers in the conduct of research with human subjects. It also highlighted the value of real-world data and evidence (RWD/E) to identify medical countermeasures and expedite their availability to patients. McKesson played an active role during the pandemic, getting critical drugs to patients and keeping pace with the supply chain, in addition to our role as the centralized distributor of vaccines and ancillary supply kits for the government. As such, we have demonstrated the ability to think creatively and overcome barriers so that patients get the care they need where and when they need it. Based on our experience in the research and clinical trial space, we have organized our comments around the following topics:

- Value of Community-Based Oncology Providers in Bridging Access Gaps
- Potential for Biomarkers to Aid Precision Medicine for Patients, Especially Underrepresented Groups
- Use of Digital Health Technologies (DHTs) and Real-World Data (RWD)
- Social Determinants of Health Data Barriers
- Leveraging Clinical Trial Networks in Community Settings Including Pharmacies
- Legal and Regulatory Barriers that Impede Access

Value of Community-Based Oncology Providers in Bridging Access Gaps

Most clinical trials tend to be centered around large academic medical centers in the more populous parts of the country, creating significant financial and logistical challenges for potential subjects in rural areas. Community-based research, including research in the community oncology space, offers an opportunity for patients in these rural settings to participate in cutting-edge clinical research, thus playing a critical role in improving cancer patient outcomes across the United States. In fact, more than 50% of patients[1] with cancer are treated in a community oncology setting. Not only do these practices provide affordable, state-of-the-art care to patients, but they do so closer to patients' homes – and to their families and support systems. **Supporting efforts to expand clinical research beyond the academic environment will allow access to a larger and more diverse patient population treated in a variety of healthcare delivery settings, which can accelerate accrual to cancer clinical trials and other human subjects research and increase the generalizability and relevance of study findings**.[2] Understanding the prevalence, care delivery patterns, and patient outcomes in communities large and small is critical to advancing our knowledge of cancer and our approach to clinical innovation.

In the guidance *Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs*[3] the Food and Drug Administration (FDA) recommends fostering community engagement, working directly with communities to address participant needs, and involving patients and caregivers in the design of clinical trial protocols. This can be easily achieved by community providers who are readily accessible and can reduce some of the financial burdens (e.g.travel access and expense, extended daycare for overnight stays) that research participants might otherwise face. **We encourage OSTP to include community-based providers in its clinical trial strategies.**

Potential for Biomarkers to Aid Precision Medicine for Patients, Especially in Underrepresented Communities

[1] https://communityoncology.org/wp-content/uploads/2017/08/What-is-Comm-Onc.pdf
[2] https://ncorp.cancer.gov/about/
[3] https://www.fda.gov/media/127712/download

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McKesson appreciates OSTP's recognition of the need to increase enrollment and retention of patients in clinical trials, especially from underrepresented populations, and to increase diversity in research and clinical trials. These steps are imperative to achieving health equity for every patient. In the United States, racial and ethnic minority populations are disproportionately impacted by cancer and cancer-related mortality, but remain underrepresented in precision oncology and clinical trials.[4] Disparities in participation may be partially attributable to lower rates of biomarker testing among racial/ethnic minorities compared to non-Hispanic white patients.[5] Enrollment of diverse participants in clinical trials, as well as the race- and ethnicity-specific reporting, can enable a comprehensive understanding of ancestry-related differences in cancer biology, disease biomarkers, or treatment responses and ensure that newly approved anticancer agents can be safely used in the real-world patient population for whom these treatments are ultimately intended.[6] **Advancing the use of biomarkers is an important step toward furthering the goals of research, including the Cancer Moonshot**.

Use of Digital Health Technologies (DHTs) and Real-World Data (RWD) is Critical to Expanding Patient Access Across Rural and Underrepresented Communities

Properly leveraging healthcare data is critical to healthcare equity. An essential first step is ensuring that clinical trial participants have access to digital health that allow for remote participation in clinical trials. Healthcare regulators and healthcare stakeholders have long recognized that digital-health solutions have the potential to promote health equity by facilitating access of health information. In particular, "mobile technologies have a unique potential to reduce disparities because of their extensive use in racial and ethnic minority communities."[7] To be most effective, real-time, secure, complete, and accurate health information must drive those technological engagements. To succeed in engaging communities, all entities involved in care coordination and clinical trials must be able to receive, use and communicate such information for large scale research and coordination among individuals and entities involved in the trial, including patients, investigators, providers, and any and all sites of care participating in a patient's care journey.

Advancing the use of digital health technologies, including real-world data collections from patients, will serve to drive better and more diverse clinical trial participation, retention and therapy regimen adherence, and of course resultant health outcomes.

There should be no unnecessary limitations on who can receive protected health information (PHI) so long as the recipient uses—and is authorized to use—the PHI to support care coordination and clinical trial participation.

Understanding Social Determinants of Health (SDOH) Barriers Are Essential to Future Clinical Research Study Designs

It is crucial that we understand how health disparities affect healthcare and identify ways to moderate the impact of social determinants of health (SDOH) data (e.g., area-level educational attainment, median household income). Studies have found that SDOH data are associated with

[4] Saphner T, et al. Clinical trial participation assessed by age, sex, race, ethnicity, and socioeconomic status. Contemporary clinical trials. 2021;103:106315.
[5] Bruno DS, et al. Disparities in Biomarker Testing and Clinical Trial Enrollment Among Patients With Lung, Breast, or Colorectal Cancers in the United States. JCO precision oncology. 2022;6:e2100427
[6] https://cancerprogressreport.aacr.org/disparities/cdpr22-contents/cdpr22-disparities-in-clinical-research-and-cancer-treatment/
[7] https://www.healthit.gov/buzz-blog/from-the-onc-desk/advancing-health-equity-digital-age

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trial participation,[8] and socioeconomic inequities may exacerbate the ability to recruit minority patients into precision oncology trials. McKesson's oncology ecosystem is currently engaged in a series of retrospective non-interventional research studies, leveraging our oncology-specific electronic health record (EHR), iKnowMed[sm], to further identify socioeconomic factors and challenges associated with germline testing and medication adherence in triple negative breast cancer. We anticipate the findings will be published later this year and intend to pursue similar efforts across other cancers. We believe this type of research is essential to supporting the clinical research community in better understanding how to design, recruit, and retain diverse patient populations. It is also essential that stakeholders continue to actively engage and advance efforts to standardize SDOH data elements, and we encourage OSTP to explore how the federal government might expedite these efforts. Finally, we want to underscore that patient perspectives are central to understanding SDOH barriers. Meaningful solutions will only come with their input and support.

Leveraging Clinical Trial Networks in Community Settings Including Pharmacies

Reimagining the clinical trial ecosystem requires a careful assessment of what can be gained by leveraging skilled healthcare workforces within the community setting. According to Pharmacy Times, 90% of the population lives within 5 miles of a pharmacy and 74% of community pharmacies are in populations of less than 50,000.[9] In these rural and underserved communities, pharmacists play a particularly essential role and often provide the most convenient point of care for these populations. By way of example, pharmacists are easily accessible medication experts who are educated in addressing questions, concerns, and problems with medications. Our seniors much prefer accessing the healthcare system through their community pharmacy as it is the pharmacist that often enjoys primacy of a trusted relationship with patients. For this reason, pharmacists can play a vital role in supporting clinical trials in the community setting; they are able to facilitate patient engagement and education, and they also can assist with developing the evidence needed to evaluate the impact of SDOH.

McKesson recommends that OSTP consider pharmacies as part of the clinical trial network to provide increased access and support for clinical trials in the community setting. However, measures should be developed to ensure that pharmacists can be successful in supporting clinical research such as funding for advanced training, setting parameters for success limited to the community partnership with physicians, and identifying and supplying the resources necessary to support pharmacists in rural communities. Finally, we want to **emphasize that the science should always drive clinical trial design and protocols necessary to ensure the integrity of the trials and patient safety.** To that end, we recognize that pharmacies may not always have the requisite resources necessary to support clinical trials. Therefore, it is imperative that federal agencies, like the National Institute of Health (NIH), National Cancer Institute (NCI) and the FDA work together to provide appropriate guidance to this evolving clinical research ecosystem so that the rigor of the trials and protections for patients is assured, while also not missing the vital opportunity to expand access to underrepresented communities throughout the United States.

Legal and Regulatory Barriers that Impede Access

[8] Alegria M, et al. Reporting of Participant Race, Sex, and Socioeconomic Status in Randomized Clinical Trials in General Medical Journals, 2015 vs 2019. JAMA network open. 2021;4(5):e2111516
[9] Ibid

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The Federal fraud and abuse laws, most notably the Federal anti-kickback statute (42 U.S.C. § 1320a-7b(b)), pose significant legal and regulatory barriers to efforts to increase diversity among study participants and to expand clinical research to underserved populations. A study by mdgroup in 2020[10] recognized that recruiting and retaining patients through the clinical trials process presents many barriers, including length of trial, study size, inadequate insurance coverage, time and travel costs for the participants, and numerous informed consent documents. These obstacles are particularly challenging for patients in underrepresented populations.[11] By allowing sponsors and those working on their behalf to collaborate with patients to identify and work with community-based organizations to remove some of these obstacles (e.g., transportation, childcare, access to digital health technologies), we can pave the way for increased participation from diverse socioeconomic and sociodemographic populations.

To address the legal barriers presented by the Federal fraud and abuse laws, McKesson recommends that OSTP consult with the Office of Inspector General (OIG) for the Department of Health of Human Services (HHS) about developing a safe harbor to the Federal anti-kickback statute that would protect remuneration offered to clinical trial participants to address the specific issues that may impede their enrollment or that they may encounter as a result of their participation in a clinical trial. An appropriately tailored safe harbor would facilitate the goals in this RFI - increasing clinical trial diversity and using digital health technologies to expand clinical research into underserved areas. Moreover, these arrangements may create efficiencies in clinical trials by minimizing participant abandonment, which could decrease the time to approval for new products that, in turn, increases competition and lowers costs to Federal health care programs. Finally, these support services have the potential to improve access to medically necessary—and often life-saving—clinical trials and to increase the overall quality of health care services provided to patients. Without such a safe harbor, the Federal fraud and abuse laws may stifle beneficial arrangements that could serve these vulnerable patients and could prolong the clinical trial retention problems that are hampering many of the goals outlined in this RFI.

Conclusion

McKesson is grateful for the opportunity to submit comments in response to OSTP's Emergency Clinical Trials RFI. We encourage OSTP to continue championing innovation across the federal research community and press the Centers for Medicare and Medicaid Innovation (CMMI) to pilot clinical trial collaborations across nontraditional sites of care, such as pharmacies. We would also note that McKesson's healthcare ecosystem has a number of exciting pilot programs underway or close to launching that relate to many of the critical public policy issues we have highlighted in this letter and would welcome the opportunity to share more details about these initiatives should OSTP be interested. If you have questions or need further information, please contact Fauzea Hussain, Vice President of Public Policy, at Fauzea.Hussain@McKesson.com.

Sincerely,

Pete Slone

[10] https://mdgroup.com/blog/why-do-patients-drop-out-of-clinical-trials/#:~:text=6%20Reasons%20Why%20Patients%20Drop%20Out%20Of%20Clinical,and%20stress%20...%206%206.%20Family%20commitments%20

[11] National Institutes of Health, Office of Research on Women's Health, *Review of the Literature: Primary Barriers and Facilitators to Participation in Clinical Research*

January 19, 2023

Dr. Arati Prabhakar
Director
Office of Science and Technology Policy
1650 Pennsylvania Avenue NW, Washington, DC 20502

RE: 87 FR 64821 | Request for Information; Clinical Research Infrastructure and Emergency Clinical Trials

Dear Dr. Prabhakar:

The Digital Medicine Society (DiMe) appreciates the opportunity to provide input in response to the joint request for information made by the Office of Science and Technology Policy (OSTP) and the Office of the National Coordinator for Health Information Technology (ONC) on the development of a scaled and coordinated clinical research infrastructure that better supports the nation's capacity to address future public health emergencies. The input provided in this document pertains to the unique opportunity for digital innovation to support the development of a more nimble and distributed emergency trials infrastructure and to increase the volume and diversity of trial sites, providers, and patients able to participate in research to address acute data needs.

DiMe is a global non-profit that partners with experts from across the technology, health care, and public sectors to conduct field-leading research and develop pre-competitive resources that accelerate the ethical, effective, equitable, and safe use of digital medical products. DiMe's portfolio spans efforts in digital measures, regulatory science, and healthcare and public health, including programming aimed at enhancing the evidence generation capacity of the clinical trials enterprise with digital medical products and increasing diversity, equity, and inclusion in digital clinical trials. Through this programming, DiMe has identified the unique capacity of digital medical technologies for supporting emergency evidence generation across a set of several basic and advanced dimensions–this is the focus of the input provided in our response.

DiMe supports both the OSTP's establishment of a Pandemic Innovation Task Force and the White House's establishment of the Steering Committee for Pandemic Innovation to address gaps in innovation and pandemic preparedness and to identify priority areas for investment. Further, DiMe applauds the work of ONC on furthering the adoption of common standards for data interoperability and exchange in research

as well as its important work on the certification of health information technologies so that they meet appropriate technical, functional, and security specifications.

DiMe also applauds the emphasis on the role of digital medical products, such as wearables, connected sensing products, biometric monitoring technologies, and more for real-time monitoring of disease and other important pandemic preparedness and response measures in the National Biodefense Strategy. This work, alongside other public and private sector efforts, will contribute to the future ability of the federal government and clinical trials enterprise to address key issues in clinical trial design and conduct that prevented an effective national response to the COVID-19 public health emergency.

Key challenges in the nation's response to the COVID-19 pandemic included issues in:

1. Activating clinical trial sites quickly enough to keep pace with rolling surges in COVID-19 rates across the country
2. Recruiting and enrolling a sufficient volume and diversity of participants in COVID-19 research
3. Providing resources to equitably address the trial participation needs for underserved communities
4. Aiding health care providers in carving out time to collect data on investigational medical products during the provision of emergency care
5. Comparing the results of multiple ongoing trials because of discrepancies in clinical outcome measures and standards for data collection
6. Collecting and leveraging real world data to inform real time decision making and an efficient public health response

Such challenges can be disintermediated, in part, through the equitable and effective implementation of digital medical technologies to support patient screening, trial enrollment, clinical data collection, and real world monitoring for product safety and effectiveness. Effective implementation of evidence-based and trustworthy digital medical products can improve our ability to:

1. Reimagine trial sites, automate data collection, decrease costs, and integrate research with care to streamline workflows and increase efficiencies
2. Decentralize research, expand trial access, and increase representative enrollment
3. Ensure efficient trial matching and surge trial enrollment
4. Leverage data collected in real world care and life settings to inform decision making

1. **Reimagine trial sites, automate data collection, decrease costs, and integrate research with care to streamline workflows and increase efficiencies**

The ability to automate and integrate aspects of clinical research with routine and emergency care delivery will be critical to improving the evidence generation capacity and representative nature of the emergency clinical trials. Federal investment in data collection infrastructure (i.e. platforms and standards) and support for the adoption of turn-key clinical trial management software that allows for the automatic transfer of patient health record data to fields in an electronic data capture system will be especially supportive of research that fits in with routine and emergency care delivery. The implementation of such software can simplify trial participation, making it more feasible for health systems and providers who don't typically participate in clinical research to be included in an emergency clinical trials network. This emergency trials network, or "warm base" that is activated, or can more quickly activate through the expedited implementation of turn-key clinical trial management software, to address priority research questions with a targeted investment in data collection infrastructure can provide trial access to patients underrepresented in research. The enrollment of such patients in emergency clinical trials can improve trial generalizability and expedite trial completion, via a larger and more representative sample of patients enrolled, and can produce information about treatment efficacy across subpopulations of interest.

To enhance the emergency clinical trials infrastructure, federal programing should consider the development of appropriate incentives for research participation, provide health system level support for technology adoption, and plan for workforce preparedness with systematic and industry-aligned training, standards, and vetting to ensure consistent quality in data collection. This will allow for trials that are quickly and sufficiently powered to produce evidence about treatment efficacy across a generalizable sample of the US population. Federal efforts should also continue to promote common Health Level 7 (HL7) Fast Healthcare Interoperability Resources (FHIR), to ensure that data automatically captured by this software meets consensus-based standards for data integration (e.g. Sensor Data Integration), interoperability, and exchange, expediting the generation of high-quality evidence to meet emergency information needs.

2. **Decentralize research, expand trial access, and increase representative enrollment**

Digital research platforms that enable telehealth visits, simplified electronic consent, and remote data collection can extend clinical trial access to a larger and more diverse group of patients. This offers an expedited and accessible pathway to higher

quality, more generalizable insights into treatment effects across subgroups representative of the nation's population. Such platforms can also reduce the administrative burden of participation in research, precluding the need to navigate complex consent and data collection processes as well as the need to travel for research visits.

Executive branch sponsors of research should consider how to effectively leverage digital research platforms for remote data acquisition to make it easier to enroll harder to reach patients and supplement the capacity of site-based data collection during future public health emergencies. This approach may be especially helpful during public health emergencies where isolation is essential to reduce disease transmission and where health systems are too overwhelmed with the care of acutely ill patients to devote resources to data collection in the clinic.

3. Ensure efficient trial matching and increase trial enrollment

Artificial Intelligence (AI)/Machine Learning (ML)-enabled screening software can accelerate understanding of disease progression and support trial matching to assist in cohort selection and patient enrollment, critical and often time consuming dimensions of clinical trial conduct. AI/ML analysis of healthcare and federal real world data/real world evidence (RWD/RWE) sources can be an integral part of protocol development and used to identify additional patients for enrollment based on specific inclusion and exclusion criteria, disease epidemiology, and patient health history. AI/ML technologies have the potential to transform the volume and speed with which we put patients on protocol, but there are gaps in the research base related to the ethics and effectiveness of algorithm driven trial matching technologies. Federal stakeholders should consider launching systematic research efforts to assess the performance of the software, including sponsoring the development of criteria for the ethical, effective, equitable, and safe use of AI/ML – and the data sets they mine –in clinical trial enrollment processes.

Other tools that simplify and expedite trial enrollment include eConsent platforms, which have tremendous potential for transforming the way patients navigate and consent to participation in an emergency clinical trial where efficiency of enrollment and decreased patient burden to support retention matters a great deal. These platforms have the capacity to reduce the administrative burden of enrollment as well as enrollment-related protocol deviations, supporting increased trial participation and speeding time to results. These tools also promote health equity, as eConsent allows for approaches that ameliorate disparities in health literacy (i.e. through the use of videos etc.) that impact trial access and enrollment. Finally, these tools can ensure more seamless design of consent processes so patients can consent to the

use and reuse of their data, as well as to participation in trials with innovative designs, important for enhancing the evidence generation capacity of the clinical trials enterprise as a whole.

4. **Leverage data collected in real world care and life settings to inform decision making**

Connected sensor technologies that support patient monitoring and remote data collection can allow us to extract insights from the wealth of continuously collected health data generated during the course of routine care delivery. These tools can also help us to efficiently gather the most essential data about medical product safety and effectiveness in real world settings outside of health systems to inform ongoing treatment decisions. Real world data generated via sensor-based technologies are especially useful in novel pandemic situations where the evidence base for what works best is limited but patients still need to receive treatment for acute conditions. To enhance our ability to leverage real time learnings from real world data generated using sensor-based technologies, federal stakeholders should consider supporting the development of guidelines, standards, and recommendations to address real and perceived deficits in the quality of real world data and to increase trust in sensor-based technologies that support real world data collection. This work would address important issues that can help unlock the promise of flows of real world data from sensor-based technologies to support emergency evidence generation that drives faster and better decisions across the healthcare continuum in real time.

DiMe firmly believes that there is value in the demonstration program suggested by OSTP. Pilots would enhance our ability to identify and resolve key issues preventing quick trial activation at scale to address gaps in the clinical evidence base. These pilots could be completed in therapeutic areas where there is an acute unmet medical need and a large and diverse patient population, such as cardiovascular disease, to ensure that their results are more broadly applicable to emergency trials. DiMe, and others, are already undertaking work to identify and scale approaches that support site readiness and expedited decision making by developing standards to guide and incentivize the adoption of digital health tools which can expedite and democratize data collection across the evidence generation life cycle.This work can be extended by federal stakeholders by harmonizing data requirements, investing in digital trial infrastructure, de-risking novel trial methods, and making the best use of the wealth of digital health data already generated by the healthcare system.

Additionally, DiMe believes there is a need for multi-stakeholder education and training to build the skills, capabilities, and trust that support successful implementation of the digital technologies mentioned above in clinical trial conduct.

To fully realize the benefits of digital tooling to support emergency evidence generation, and evidence generation more broadly, the need for change management and workforce training is as important as efforts to develop technologies and infrastructure that have the potential to transform trial conduct. To ensure successful implementation – and to enable the clinical trial enterprise to address acute data needs – we have to define the value of digital technologies within R&D, communicate this value across stakeholders, and equip them with the necessary knowledge, tools, and experience to better execute their roles with the help of digital tools.

Finally, DiMe emphasizes that many of these recommendations to enhance emergency clinical trials offer the positive externality of a more modern, robust, sustainable, and equitable trials infrastructure outside of the public health emergency context. Appropriately leveraging digital tools to better integrate medical product development and biomedical research into routine clinical care will improve our collective ability to respond to viral public health emergencies, but also to the public health crises of health inequity, healthcare costs, and declining life expectancy.

DiMe commends OSTP for taking this important step to improve the readiness of the clinical trials enterprise to address emergency data collection needs and welcomes further questions about the input we have provided. DiMe also welcomes the opportunity to collaborate with OSTP and ONC on the development and implementation of validated standards and frameworks for digital innovation to further support the evidence generation capacity of an improved emergency trials infrastructure.

Please direct any follow-up to this letter and other related topics to sarah.sheehan@dimesociety.org

Sincerely,
Jennifer Goldsack, MChem, MA, MBA, OLY
CEO, DiMe

on behalf of:
Sarah Sheehan, MPA, Program Lead, DiMe
Smit Patel, PharmD, Program Lead, DiMe
Yashoda Sharma, PhD, Program Director, DiMe

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VIA ELECTRONIC DELIVERY

December 19, 2022

Emergencyclinicaltrials@ostp.eop.gov

RE: Request for Information; Clinical Research Infrastructure and Emergency Clinical Trials:

Dear Sir or Madam:

Eli Lilly and Company (Lilly) is pleased to provide comments on the White House Office of Science and Technology Policy and National Security Council's Request for Information on clinical research infrastructure on emergency clinical trials (RFI).

During the COVID-19 Pandemic Lilly provided leadership and innovative solutions in our approach to conducting clinical trials during the ongoing pandemic. Lilly is uniquely situated in that we were able to quickly obtain Emergency Use Authorization for COVID-19 monoclonal antibody treatment. Given the uncertainty around potential future health emergencies, it is helpful to receive input from a wide variety of product manufacturers and participants.

Lilly is a global healthcare leader that unites caring with discovery to make life better for people around the world. We were founded more than 140 years ago by a man committed to creating high-quality medicines that meet real needs; and, today, we remain true to that mission in all our work. Across the globe, Lilly employees work to discover and bring life-changing medicines to those who need them, improve the understanding and management of disease, and give back to communities through philanthropy and volunteerism.

Lilly has provided responses to select questions below.

1. Governance for emergency clinical trials response.

1. f. Procedures whereby the U.S. Government, together with external stakeholders, could oversee the development of clinical trial protocols and, where appropriate, the selection of investigational agents. It would be particularly helpful to get input on whether there is a role for public-private partnerships in this context.
Lilly Response: Partnerships between public and private entities can often be beneficial, especially in terms of providing information/data that an organization would not have previously

had access to (i.e., FDA and RWE). However, it would be important to establish timelines and understand the speed at which each organization is able to move. Lilly has experienced certain situations where a slower moving partner has slowed the speed of a clinical trial. It would be important to select entities that are able to clearly communicate their timing and capacity at the outset to allow them to match the speed of work with the corresponding partner. Additionally, optionality is important (e.g. do not require it as a mechanism of development).

1. g. Best practices, including "quality by design" principles, for designing trials so that they capture the data needed without unnecessary complexity that can complicate execution.

Lilly Response: Reducing complexity of data will be imperative to achieve during a potential health emergency. Ensuring data collection is limited to that necessary to support key primary and limited secondary endpoints is critical. Utilizing both technical and therapeutic platform knowledge could accelerate development and support "quality by design" principles.

1. i. Optimal ways to manage interactions with domestic and international regulatory bodies.

Lilly Response: As we have experienced with the COVID-19 pandemic international effort is critical. In terms of clinical trials specifically this program could do so by promoting, further developing, and utilizing mutual reliance programs related to data review and trial design as well as consistent standards for leveraging decentralized capabilities to ensure optimal recruitment and retention.

2. Identifying and Incentivizing Research Institutions and Networks; Building Diversity and Equity.

2. a. Methods for identifying institutions and sites that may have an existing interest in or familiarity with emergency clinical trial research. This might include those that currently receive government funding, those with a focus on infectious disease research, and/or those that have worked with CROs.

Lilly Response: In an effort to identify and engage institutions quickly in an emergency clinical trial situation, this program could utilize of internal/external dataset to understand those that have participated in previous EUA trials. Additionally, this program could engage those participants that already involve community research networks. However, it is important to note during COVID-19, most engaged sites were in the highest prevalence areas. Learning here is that investigator identification is secondary to patient prevalence and more investigators can participate beyond those that are involved in traditional site/investigator studies.

2. b. Effective ways to increase diversity among study participants and investigators, and to expand clinical research sites into underserved areas. It would be helpful to get input on whether and how the following approaches could be useful:

i. Community outreach:

Lilly response: Gaining trust within communities of interest is vitally important to the success of clinical trials. This program could succeed in these community outreach activities by: providing mobile screening, leveraging trusted intermediaries/community connectors, education

campaigns, leveraging census and disease prevalence information to understand location of potential participants as well as clinicians/investigators, ensuring patient facing vendors are diverse and/or have a strategy to reach diverse populations, and developing specific recruitment strategies for diverse populations within specific geographies/communities.

ii. Use of decentralized clinical trial (DCT) design elements, or other innovative approaches such as trials conducted at the point of care

Lilly Response: Enabling trial conduct within communities is important to the use of decentralized clinical trials. Trial participant burden (and likeliness to continue with a trial) can be quantified by distance to sites and visit time. The willingness to continue to participate in a trial drops by half with each additional doctor visit and many patients state the distance to clinical sites as a major barrier to participation in trials (*Source: LabCorp Patient Intelligence Database*). This burden can be reduced by the inclusion of DCT design elements, which includes, but is not limited to telemedicine, mobile/remote screening, local lab, imaging, and infusion centers. It is important to design trials that can be done fully or in part in a decentralized manner and complete systematic reviews of inclusion/exclusion criteria to decrease burden and ensure equal access to participation.

iii. Use of technological innovations, such as digital health technologies (DHTs), that would allow remote participation or otherwise limit the need for participants to travel

Lilly Response: In order to accomplish a decentralized approach, equal access to applicable technology and WIFI/infrastructure must be addressed. Also, sponsors must develop simple platforms that allow for streamlining of assessments (one stop shop) and utilize acceptable validated endpoints for remote assessments.

iv. Building on existing programs that target diversity in clinical research, including initiatives within research institutions and public-private collaborations

Lilly Response: Building on existing programs to target diversity in clinical research is possible by leveraging specific advocacy groups, funding for minority physicians to become PIs, or providing funding for strategic partners to establish clinics for trial access (e.g., long term care facilities/retirement communities). Also, this program could provide supplemental government funding for ongoing programs to maintain/expand.

6. International coordination and capacity.

6. a. Designing the overall domestic emergency clinical trials effort in a way that coordinates with international clinical research efforts. It would be helpful to receive comments on how to facilitate the participation of foreign-run clinical trial networks and other foreign bodies in coordinated, large-scale emergency clinical trial protocols initiated by the U.S.

Lilly Response: This program could support and leverage the work of International Coalition of Medicines Regulatory Agencies (ICMRA), the International Council on Harmonization (ICH), and the World Health Organization (WHO), which attempt to coordinate and align regulatory

requirements. The FDA actively participates in these forums, and they could continue to be leveraged in a future pandemic situation.

6. c. Overcoming regulatory barriers that delay expansion of U.S. trials into international sites, or otherwise interfere with clinical research across borders.
Lilly Response: Regulators should develop methods for optimal cross agency communication practices to be used during a pandemic, keeping in mind current patient and commercial confidentiality.
This program could support and pursue regulatory infrastructure improvements globally, particularly for LMICs. For example, advance cloud-based submissions where sponsors can share data with all regulators in real time. Facilitating early pandemic alignment across regulatory agencies and improve sharing of clinical study protocols, surrogate endpoints, and other data to support to EUAs will be important.
Overall, In the interest of better future pandemic preparedness, global leaders need to work toward an approach that, at the outset of an emerging pandemic, would enable more efficient and coordinated scientific information sharing, clinical and regulatory priority-setting, and frequent (i.e., weekly) communication of evolving knowledge and recommendations. This recommendation extends beyond, but applies to, clinical trials preparations and global coordination.

6. d. The best way to track the clinical trial research initiatives being pursued under the G7 Trials Charter and Quad leaders' commitment to pandemic preparedness, and to harmonize U.S. emergency clinical trials efforts with these international initiatives.
Lilly Response: There is need for a global group of technical experts, with a dedicated process, to drive toward pre-pandemic preparation and more cohesive and consistent information sharing and priority-setting during a pandemic to support efficient development and use of a range of diagnostic, prevention, and treatment options. The group could be coordinated under the auspices of the ICMRA, the ICH or another emerging organization. One role of such a group could be to facilitate this type of G7 Trials Charter coordination.

In closing, we appreciate the opportunity to provide written feedback to the important question posed in this RFI. We would like to continue to be a partner in developing and executing this clinical research infrastructure. Please don't hesitate to reach out if you have any questions or need further information.

Respectfully submitted,

ELI LILLY AND COMPANY

Janelle A. Sabo
Senior Vice President
Clinical Capabilities
Eli Lilly and Company

PPD's Repsonse to the Clinical Research Infrastructure and Emergency Clinical Trials Request for Information (RFI) from the White House Office of Science and Technology Policy (OSTP)

RFI Due Date: January 27, 2023

Original

PPD Development, LP, Part of Thermo Fisher Scientific
929 North Front Street
Wilmington, NC 28401
Matthew Kirkby, Executive Director, Contract Administration
Phone: 910.558.6868; Email: Matthew.Kirkby@ppd.com
UEI: ZANENSW6C665

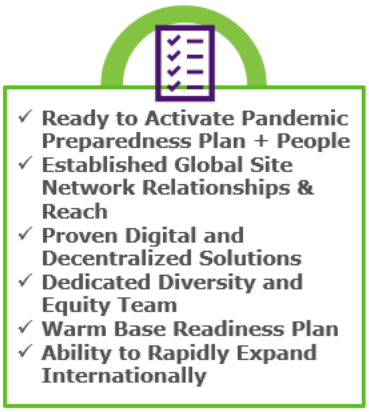
Matthew Kirkby, Executive Director, Contract Administration

Executive Summary

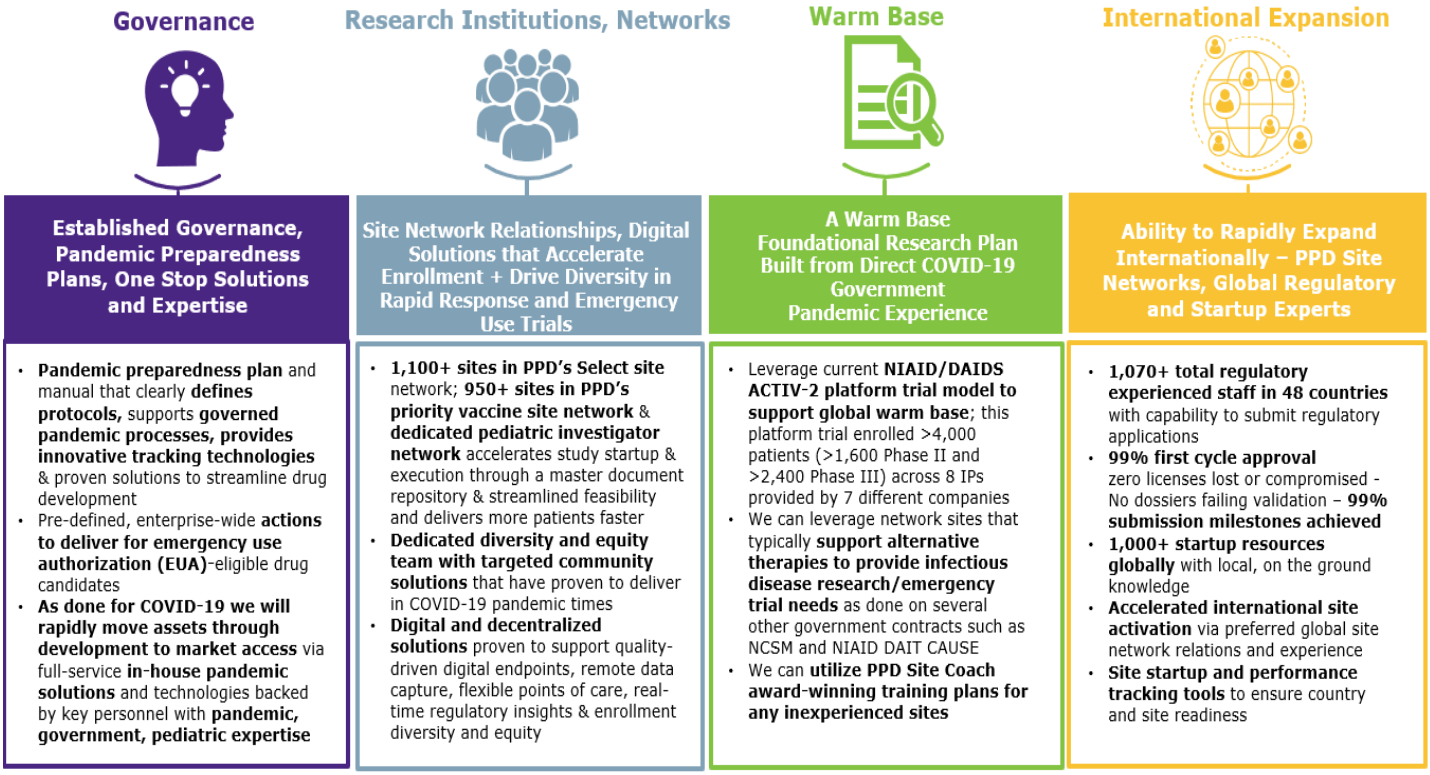
The White House Office of Science and Technology Policy (OSTP), in partnership with the National Security Council (NSC), is seeking an expert partner to govern, lead and support outbreaks of disease and other emergencies via a wide range of institutions, clinical trial networks, and other potential trial sites that can participate in emergency research, both domestically and internationally. OSTP will benefit from a partner that can also expand clinical research into underserved communities and increase diversity among both trial participants and clinical trial investigators.

PPD, the Clinical Research Group of Thermo Fisher Scientific, can confidently support OSTP's Emergency Clinical Trial initiatives leveraging award-winning pandemic preparedness knowledge gained from being an industry leader in COVID-19 asset development since February 2020.

With ~ **$2B in COVID-19 awards to-date including ~320 COVID-19 clinical studies and consulting agreements**, of which **> 225 are vaccine and treatment studies** spanning all operational functions, our global reputation for pandemic vaccines, diagnostics and therapeutics expertise coupled with **30+ years of federal government experience**–we can deliver results for OSTP's emergency research needs in unprecedented and industry-leading ways.



Our **directly aligned** and **exclusive pandemic experience** includes supporting **Moderna's 30,000+ patient COVID-19 mRNA vaccine product development program** and **NIAID DAIDS' ACTIV-2 COVID-19 investigational product Phase II/III outpatient master protocol platform.** We have also developed an **accelerated process parallelization pathway** to go from **mRNA raw materials to clinical trial start in ~100 days in a pandemic scenario** for one of our Top 10 pharma partners. From this unmatched, in-house expertise we can provide OSTP partnership benefits that include:

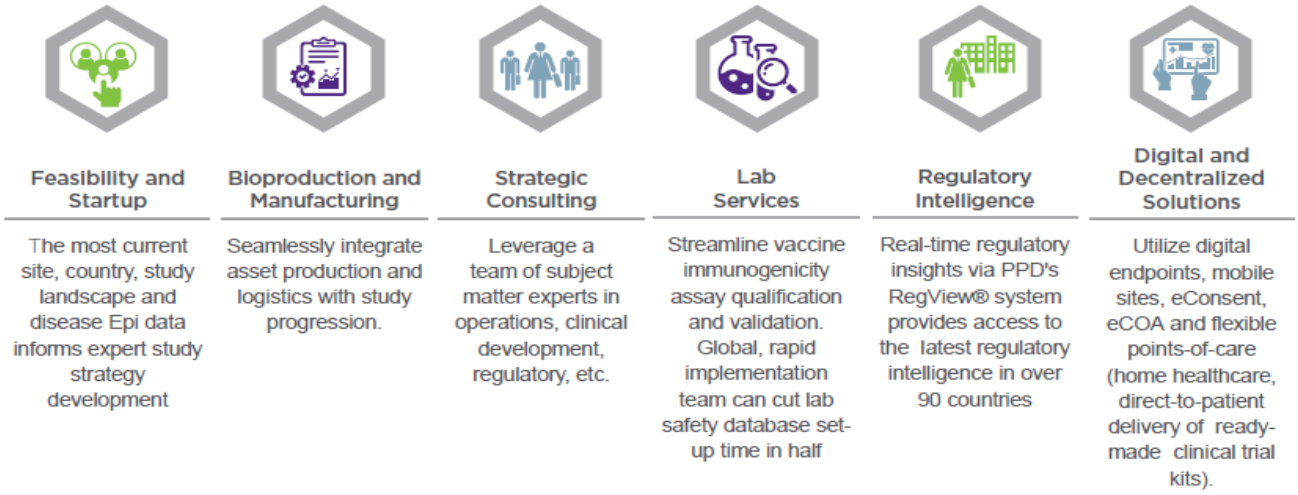


As your CRO partner we can accelerate clinical research while saving time and resources under compressed timelines. We can proactively reduce the risk of your program design with enterprise-wide pandemic knowledge and deliver enterprise-wide solutions and established processes that can save and better patient lives around the globe.

1. Governance for Emergency Clinical Trials Response

PPD has developed a pandemic preparedness, rapid response delivery model and internal execution plan which compiles processes from successes and lessons learned during the COVID-19 pandemic (see https://www.ppd.com/therapeutic-expertise/vaccine-development/pandemic-preparedness/).

This model uses clearly defined protocols, governed processes, innovative tracking technologies and solutions to streamline drug development and acts as an enterprise-wide action plan to deliver. As done for the COVID-19 pandemic, our formal delivery model can be implemented quickly for emergency use authorization (EUA)-eligible drug candidates, rapidly moving these assets through development to market access. This proactive, streamlined approach to producing medical countermeasures will enable drug developers to readily respond to forthcoming public health emergencies. Below are a few examples of in-house PPD and Thermo Fischer expertise and enterprise solutions we can leverage:



PPD developed an accelerated pathway with our Top 10 Pharma partner to go from mRNA raw materials to clinical trial start in ~100 days in a pandemic scenario - saving 9+ development months

Our robust full-service model is designed to support effective methods for communicating the decision to begin emergency clinical research alongside familiar/preferred clinical trial networks and institutions that can participate in carrying out the emergency research as well as support optimal ways to manage interactions with domestic and international regulatory bodies.

It also supports centralized methods to track data and analytics via:

+ Disease dashboards and modeling to track impacted sites/monitoring visits and adapting analyses to consider pre vs post pandemic rates to assess added risk.
+ Custom reporting for clients (key risk indicators, compliance, dashboards).
+ Data mapping can replace study data tabulation model for effective processing.
+ Pandemic-related deliverables prioritized (reports, quality tolerance limits (QTL), meetings).
+ Modified centralized monitoring plan (CMP).
+ Change scope/frequency of key risk indicators (KRI) and clinical supplies management (CSM) standard for centralized statistical monitoring.

From our pool of more than 154,000 PPD/TFS employees worldwide, we have access to leading experts in government-backed research, pandemic preparedness, infectious diseases & pediatrics.

These key personnel, coupled with a deep pool of operational subject matter experts, can provide ways of selecting the adequate number of sites needed to execute clinical trials in case of emergency, support protocol concept and design development, provide best practices for including quality design principal for effective quality-backed data capture needs as well as enrolling vulnerable populations, such as pediatrics. A sampling of these key experts, including core pandemic committee and planning members, are provided below:

Anza Mammen, Jr., MD, FACP, FIDSA
Global Product Development, Infectious Diseases

- ✓ Former biotech executive and retired Army colonel; lead development of the "Pandemic Warning Team" within the Army, AFRIMS in Thailand for 5 years, and as the Integrated Product Team Lead worked on Dengue vaccine development for the military
- ✓ 24+ years' experience in vaccine development, global health, and program management
- ✓ Engagement of key opinion leaders (KOLs) for the development of clinical development plans, clinical protocols, investigators' brochures, and informed consent forms
- ✓ Former Senior Vice President, Clinical Development, Biotech Companies (Vical, Inovio)
- ✓ M.D. from Pennsylvania State University College of Medicine, Hershey, Pennsylvania, USA; Internship, residency, fellowship at Walter Reed Army Medical Center, US National Capitol Area

Sandra Palleja, MD
Executive Medical Director, Global Product Development, Infectious Diseases

- ✓ 25+ years of pharmaceutical experience, Phase I through Phase IV, and has served as Academic HIV physician and researcher for 23 years prior to industry; 8 years with PPD
- ✓ Experience primarily in antivirals, including all drug classes in HIV, as well as programs in SARS-CoV-2, HCV, HBV, CMV, HPV, HSV, RSV, other infectious diseases indications including anti-infectives, and compounds unrelated to infectious diseases therapeutics.
- ✓ Leading PPD's Monkey pox committee
- ✓ Has supported and worked in biopharma, biotech and in the US public health arena

Susan McCune, MD
Vice President Pediatric and Rare Diseases Center of Excellence of Global Product Development

- ✓ Pediatrician and neonatologist with 35+ years of experience in academic medicine, bioterrorism, basic science and regulatory review and leadership, most recently as the director in the Office of Pediatric Therapeutics in the Office of the Commissioner, FDA
- ✓ Extensive experience in pediatrics (multiple indications), rare diseases and biomarkers
- ✓ Depth of expertise includes regulatory consulting for all phases of pediatric trials including review of study protocols and analysis of data submitted to the FDA
- ✓ Holds a Bachelor of Science degree from Harvard University and a Medical Degree from George Washington University; Board-certified in pediatrics and neonatology

Vanessa Elharrar, MD, MPH
Advanced Therapies Business Lead

- ✓ More than 16 years of Phase I-III trial experience and is board-certified in preventative medicine
- ✓ ~15 years combined supporting NIH Office of the Director, Office of AIDS Research (OAR), and NIH/NIAID/Division of AIDS - Prevention Science Program/ Clinical Prevention Research Branch
- ✓ Supports PPD's pandemic preparedness emergency response team
- ✓ Extensive experience with infectious disease and prevention studies, COVID-19, antiretroviral pharmacokinetic/pharmacodynamic and safety studies, and injectable and oral study products

PPD also has a dedicated strategic consulting and master protocol working group (MPWG) that focuses on study design to planning and implementation, helping reduce complexity and timelines, and improve operational efficiency for emergency use and non-emergency clinical research. Our consulting team ensures additional inputs from other functional areas are considered based on a well-defined infectious disease/vaccine focused consulting model (i.e., operations, labs, PVG, etc.) and recognizes the resource constraints and limitations to scale-up that are created when responding to an emerging pandemic. They can support implementing a plan for resource shifts and create consulting redundancies.

In the past five years, PPD has conducted 112 studies (13 platform) under master protocols including studies in COVID-19 & pediatric patient populations.

As OSTP is aware, platform studies optimize trial infrastructure, leading to key client benefits including shortened timelines, reduced costs and improved probability of success which is highly important for emergency clinical research. This approach was demonstrated in ACTIV-2's Phase II/III platform trial, where efficiencies in shared governance, shared systems for data capture and review, common trial networks, shared processes and benefits from shared best practices/lessons were applied. ACTIV-2 platform design provides patient benefits as well by better allocating patients to the most promising treatments, enabling efficient study of asset combinations across organizations, and increasing site performance through standardization. PPD's master protocol working group developed core ACTIV-2 study documents needed to successfully execute the platform trial which includes the informed consent form (ICF), patient facing documents, as well as recruitment materials.

PPD can utilize the established systems, proven processes, and developed plans from the ACTIV-2 contract to ensure efficient consultation, planning and startup are achieved for OSTP's initiative.

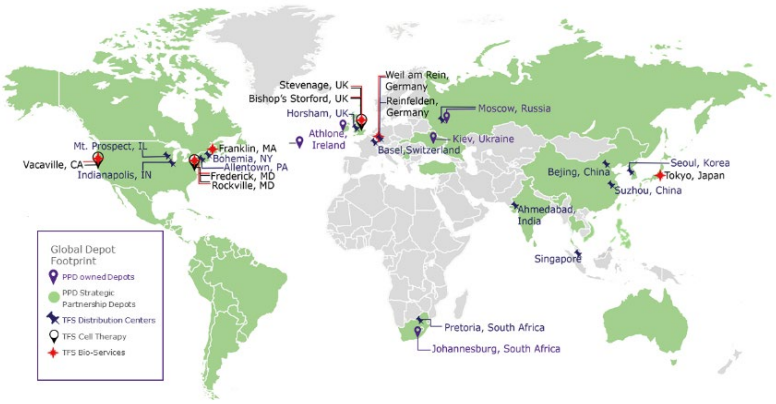
PPD' laboratories are governed & prepared to deploy data repositories & a biorepository for emergency clinical trial data & specimens handling for future pandemic, epidemic or rapid response trials.

This includes, but is not limited to:

+ Streamline vaccine immunogenicity assay qualification and validation processes to shorten timeline.
+ Use global rapid implementation team (GRIT) to cut lab safety database set-up time in half once specs are finalized and kits are shipped.
+ Implement technology (Microsoft HoloLens) to facilitate real-time assay training when face-to-face is not possible.
+ Central and Bioanalytical lab data which is housed within a blinded lab database with direct overnight feed to a data pool (pulled nightly), eliminating stop and start data transfers.

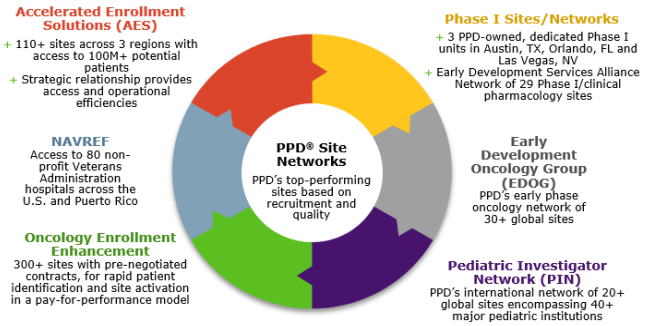
We bring OSTP more than 30 years of global clinical supplies expertise- our operational footprint includes 30+ depots worldwide.

Coupled with our long-standing knowledge of ancillary sourcing and supply chain management, this global operational footprint will provide a robust network to support the receipt, storage, distribution, relabeling, return, accountability and destruction coordination services, which streamlines the logistics associated with ancillary supply distribution needs for pandemic and rapid response trials.

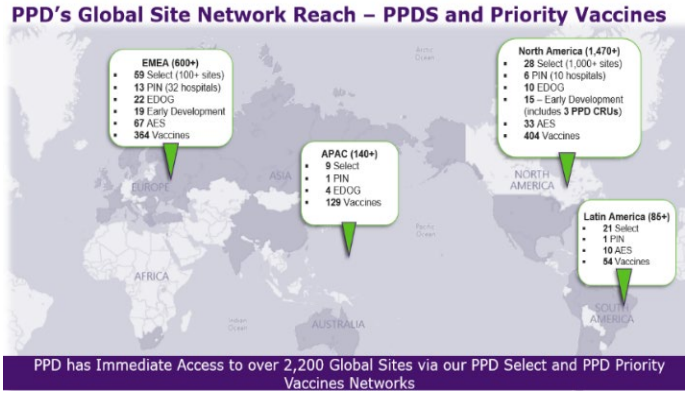


2. Identifying and Incentivizing Research Institutions and Networks; Building Diversity and Equity.

PPD continually nurtures and expands its strategic partnerships with leading US, international and government-known research sites, academic institutions, site networks and pharmacies *(i.e. CVS with recruitment access to 123MM+ through CVS pharmacies, MinuteClinics, HealthHUBs, and Aetna Insurance (all 50 states, including Puerto Rico)* to optimize patient access and deliver top data quality. PPD-owned sites, established PPD Select site network partnerships (including pediatric investigator network) allow for efficient study startup and execution through a master document repository and streamlined feasibility and contracting. This expedited start-up allows for more open site enrollment months and optimizes patient recruitment capabilities. ***When leveraging these sites we have seen 30% faster site activations and enrollment of 2.5 times the number of patients over traditional sites.***



PPD partners with a variety of other site networks and institutions to support specific geographies and indications



PPD has Immediate Access to over 2,200 Global Sites via our PPD Select and PPD Priority Vaccines Networks

PPD's Select (PPDS) and Priority Vaccines networks alone offer access to more than **2,200 pre-established site relationships around the globe that support all phases of product development**. Many of these network sites are considered top performers on COVID-19 vaccine and treatment trials and have outperformed traditional sites in the industry.

The following case study illustrates the depth of PPD site network performance and experiences gained through supporting ACTIV-2's Phase II/III extensive site feasibility, rapid startup and enrollment needs at NIAID and PPD preferred site networks.

PPD's Extensive Feasibility and Preferred Site Networks Drive Accelerated Startup, Deliver 3X Faster than other Site Networks and More Patients on NIAID/DAIDS-ACTG COVID-19 ACTIV-2 Platform Trial

Case Study

Background

- COVID-19 treatment master protocol, **>4,000 patients enrolled** (>1,600 Ph II + >2,400 Ph III) across **8 IPs** provided by **7 different companies** over **18-month period, including active comparator arm**
  Targeted feasibility:
  - **400,000 global sites** considered via PPD database assessment, **7,000 sites contacted** (**23,000+** communications made), resulted in **1,000 sites interested**, **447 sites qualified,** and **263 sites activated** across **22 countries**.
    Site networks include:
    - **ACTG** - 38
    - **PPD Select Sites (PPDS)** - 24
    - **PPD AES** - 9
    - **Transcelerate** - 6

PPD Site Network Results

- ✓ PPDS network sites activated in approximately **105 days based on master CDAs and contract templates already in place**
- ✓ PPDS network sites enrolled more patients at fewer sites **1.5X to 3X faster than other site networks**

Startup & Enrollment Challenges

Feasibility and Site Selection

- Finding sites with the ability to support IP handling with varying routes of administration
- Finding sites with dedicated areas to see COVID positive patients
- Selecting sites meeting government requirements/qualification needs
- Varying protocol requirements led to the largest feasibility ever performed at PPD

Adapting to the COVID-19 Landscape:

- **Epidemiology Changes:** fluctuation in patient population potential based on virus evolution and roll out of vaccination programs per country
- **Limited IP:** limitation on regional recruitment in specific phases for certain IPs, due to IP provider restrictions, IP availability, country approved devices to be utilized in administration of IP
- **New lab requirements:** local lab attestation needed for Ex-US sites for COVID-19 testing
- **Equipment limitations** (e.g., Laminar flow hoods) due to the pandemic supply chain issues
- **Ever changing platform design:** the strategy was constantly changing, due to data safety monitoring that stopped some IPs and progressed others. Sites had to adapt to multiple amendments and protocol design changes

PPD Strategies

- **Seamless PPD startup team approach** – PPD's feasibility, startup, clinical and leadership team aligned from inception - it was critical to have communications prioritized to expedite startup and enrollment timelines
- **PPD worked very closely with DAIDS to make swift and data-driven decisions** on site selection needs
- **Included 24 top-performing PPD Select (PPDS) sites, 9 PPD owned AES sites and 6 Transcelerate sites resulting in** expedited startup through master CDAs/ & pre-established site relationships
  - ***PPDS sites outperformed other site networks 1.5-3X faster on enrollment goals (p/s/m) – See below***
- **Utilized 38 ACTG sites** with positive DAIDS' network experience and sponsor contacts to expedite study reviews, decisions to facilitate activation to support recruitment goals
- All other sites chosen via extensive/targeted feasibility; these sites are **performing exceptional on the trial (~2.8 p/s/m)**
- **PPD internal data innovation team developed custom dashboards to track trial performance** which gave the team the ability to oversee the critical startup activities and enrollment performance across all sites

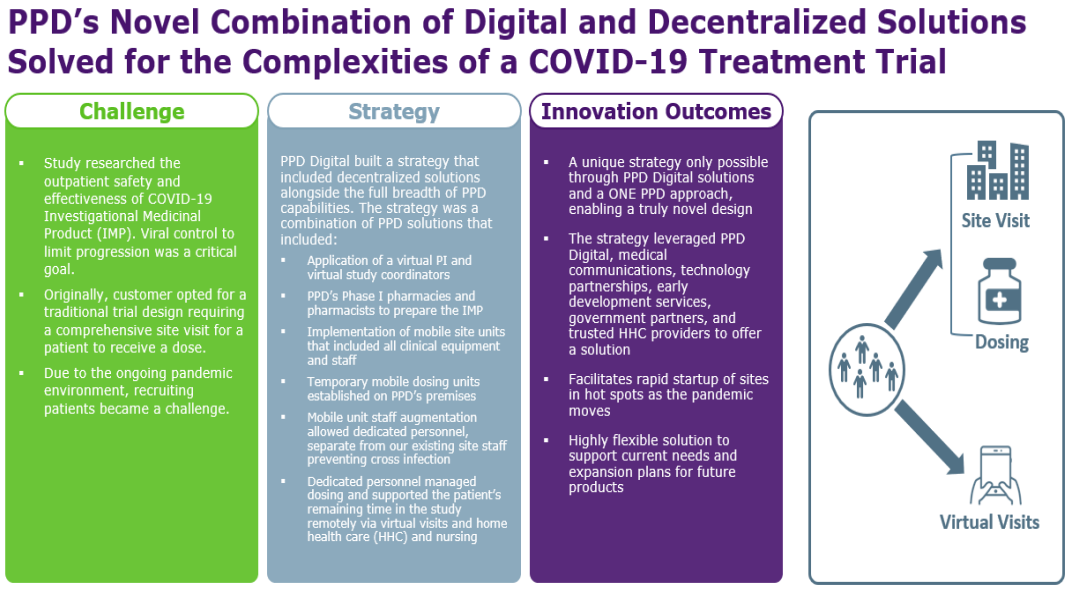
Partnership Solid Foundation. Top-tier Results.

3

Digital and Decentralized Solutions (D&DS) to Improve Patient Access, Enrollment and Experience

The COVID-19 pandemic presented us with the opportunity to transform the way we deliver studies. D&DS assigns a digital& decentralized consultant to engage early to ensure that protocols are written with the needed flexibility to allow for different methods of trial design (i.e. home visits, direct-to-patient supplies, electronic Patient Recorded Outcomes (ePRO)) as situations arise that would limit a patient's ability to access the site. We offer:

+ *Digital Solutions* — electronic consent (eConsent) and/or electronic clinical outcome assessment (eCOA), televisits
+ *Near Patient Solutions* — depending on the needs of the study, home health care and mobile research sites can be deployed, including community options such as retail pharmacies.



+ Direct-to-patient delivery of ready-made clinical trial kits (trial-in-a-box).
+ *Robust digital support systems* — provide virtual support resources and digital training modules.
+ *Real-time regulatory insights* — The PPD RegView® system provides access to the digital repository, including the latest regulatory intelligence in 70 countries (updated monthly) for the following D& DS: direct-to-patient, eConsent, remote eConsent, home health care, remote source data verification and telemedicine.

Our digital solutions increase patient access and data quality while decreasing cycle times for our clients. Our solutions patient centric, improving experience. An optimal strategy is then developed to ensure that both our sponsor's goals and their patients' goals are met.

Strategies to Ensure Diversity and Equity is Established and Maintained in Clinical Research

PPD offers OSTP a Diversity in Clinical Trials (DiCT) Steering Committee to ensure the importance and rationale of clinically relevant study populations are embedded within clinical trials.

PPD understands the utmost importance of targeted, intentional outreach and engagement strategies to improve inclusion of underrepresented groups. Our DiCT, coupled with PPD's operational product development experts, can support sites by assessing protocols for demographically appropriate inclusion/exclusion criteria and providing broadened and inclusive study design recommendations that can help reduce financial and operational burdens for participants as well as sites.

Targeted site selection based on the analysis of the epidemiology data and prevalence of the disease allows for the lens of diversity and inclusion to be embedded in the lifecycle of study from the very beginning. Information gathered through our enhanced feasibility analysis aids in developing a strong strategy and leads to the identification and strategic placement of sites.

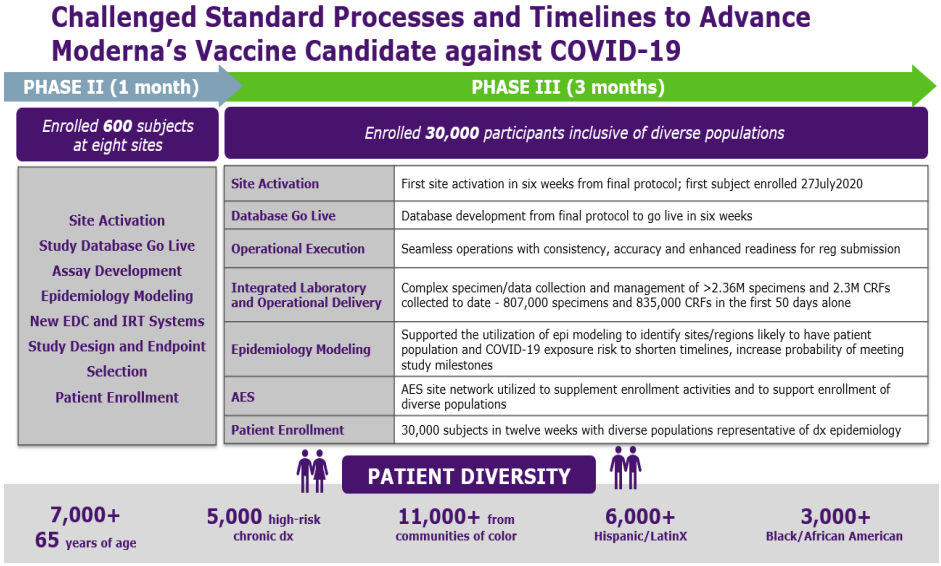
Proven strategies for engaging diverse populations include:

+ Establish rapport with minority communities, including engaging trusted referring physicians in underrepresented communities Include sites in minority communities to facilitate an increase in the number of external referrals and simplify participation logistics.
+ Encourage research institutions to embrace community activists, church groups, etc. to form partnerships and build trust.
+ Include marketing campaigns using media such as radio advertisements, commercials and fliers to increase visibility and enrich enrollment.
+ Formalize efforts, such as the use of community health advisors, to offer tailored education about clinical trial participation.
+ Increase the availability of site personnel, such as nurses or lay navigators, to address practical needs, including transportation or lodging, to facilitate participation.

By deploying these strategies, PPD helped our client increase from 2% to the goal of 20% diverse patient population in-stream for a 30,000-patient study.

We have also invested and will continue to invest in the following areas to support these efforts:

+ Providing education to PPD project teams, all Top 50 pharma companies and 300+ biotechnology companies, regarding the importance of diversity in clinical trials.
+ Leveraging proprietary and licensed data sources to identify population demographics and sites who treat higher numbers of minority patients.

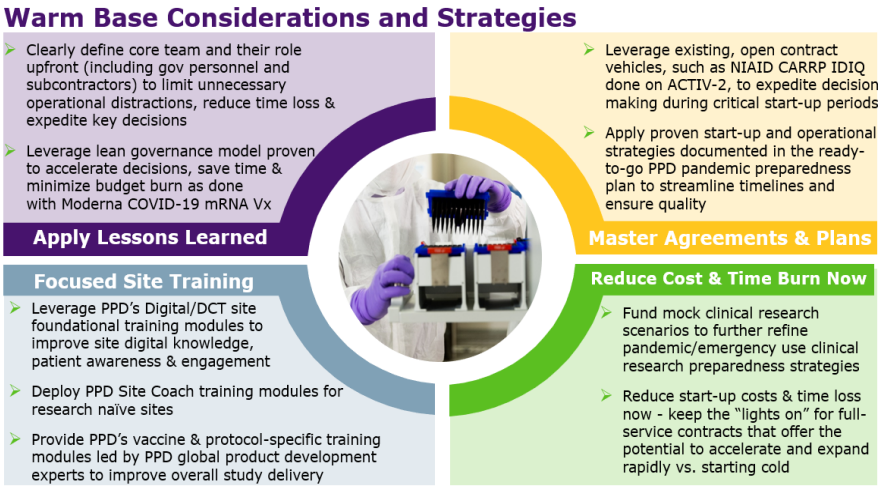


+ Site placement strategies that include new site development to reach more minority patients closer to where they live.
+ Developing minority physicians and healthcare professionals into clinical researchers.
+ Partnering with professional and patient organizations, such as National Minority Quality Forum (NMQF) to develop educational resources that will resonate with minority groups
+ Developing creative ways to reach more subjects through trusted sources like churches, health advocacy and civic organizations, barbershops and beauty salons.
+ Leveraging community advisory boards to provide guidance on subject recruitment strategies.
+ Using our own proprietary database of volunteers who have provided race and ethnicity information
+ PPD employees have access to our Creating an Inclusive Culture learning module, a resource that addresses topics foundational to Diversity, Equity, and Inclusion (DEI).

3. "Warm Base" Research

PPD can leverage direct experience gained from supporting the NIAID ACTIV-2 platform trial as a warm base for this initiative past October 2024.

By leveraging the full service ACTIV-2 contract experiences gained for this initiative, coupled with PPD's robust overarching pandemic preparedness planning strategies, we can ensure a robust warm base foundation is available and ready for emergency clinical research operational success.



6. International Coordination and Capacity

In addition to the established international site network relationships and emergency clinical research preparedness noted above, PPD's one-stop-shop offers local regulatory and startup expertise to help navigate regulatory approval and market access for your products as well as overcome international regulatory barriers that delay expansion of domestic trials into international sites. For >30 years PPD has been providing regulatory and startup services to many clients, including most of the top 30 pharmaceutical companies, biotechnology and many government agencies, and for a wide range of regulatory and start-up functions including strategy and planning; supporting interactions with regulatory authorities, marketing authorizations, lifecycle management, clinical trial applications, chemistry manufacturing and controls (CMC) projects; non-clinical support; regulatory intelligence; publishing; and site startup and submission management.

Our regulatory team is made up of more than 1,000 experts around the globe with 300 country intelligence coordinators (CICs) who are experts in local requirements and processes.

From this experience we can leverage:

+ Global regulatory network —. Each associate works closely with the local regulatory affairs and has established relationship which was leveraged to support regulatory intelligence collection.
+ Rapid RI collection and dissemination — made possible due to the availability of the in-house, proprietary regulatory intelligence platform, PPD RegView®. This is a customized, in-house database with full audit trail (PQ-validated) tailored to collect and disseminate specific intelligence via "one click access". PPD utilized the existing RI model to gather and assess intel from agencies and expand the library of COVID-19 related RI. PPD RegView® was configured to include fields to enable more granular intel, covering a large range of data collected from 99 countries.

PPD offers OSTP 1,600+ start-up resources that have a thorough understanding of local language, regulations and COVID-19 pandemic working practices to expedite study startup needs.

Our targeted feasibility and a technology-enabled approach to site selection, along with optimized startup processes, patient recruitment and industry-leading site activation, supports our startup team's singular focus in driving accelerated timelines, maximizing open site enrollment months and optimizing cycle times. The specific tactics applied to support a step-change in site activation and time to FPI include:

+ Working closely with client local affiliates to align on the optimal regulatory submission strategy; cross-regional support where one region can support after working hours.
+ Regulatory document turnaround time review in 24 to 48 hours; specific waiver of prerequisites for site activation; remote capabilities for site initiation visits (SIV)/training.
+ Close collaboration with sites and ethics committees (ECs) to discuss possibility to convene emergency institutional review board (IRB) meetings.

Medable

Medable, a clinical trial service provider, is contributing a response to the Office of Science and Technology Policy's Request for Information (RFI) on Clinical Research Infrastructure and Emergency Clinical Trials (document citation number 87 FR 64821).

Medable is a Software as a Service (SaaS) technology company with a digital platform that brings together– and streamlines– the design, recruitment, retention, and collection of data for decentralized trials in one platform. It was founded by Dr. Michelle Longmire in 2012 after she had experienced inefficiency and quality issues with traditional clinical trials as a principal investigator (PI) for rare disease trials at Stanford. Medable's responses will primarily address issues related to decentralized approaches.

Medable believes research is for everybody, everywhere: Inclusive healthcare and access to clinical trials should be a human right and participation should be easy. Innovative clinical trial modalities, such as decentralized clinical trials (DCTs), support this vision and accelerate science, enable faster cures and facilitate collaboration.

Medable offers the following decentralized solutions in a single platform and data flow structure: digital and decentralized screening, eConsent and TeleConsent, ePRO / TeleCOA (as well as patient diaries and daily reminders), TeleVisit, remote monitoring / connected sensor integration, and study management. Our platform meets the necessary standards for privacy, security and regulatory compliance for global clinical trials. Data flows together in an interconnected system, rather than as a patchwork of different technologies.

As a transformational leader in DCTs, Medable is committed to generating evidence and best practices about DCT, with our dedicated science team working closely with commercial, delivery and product teams to drive responsible adoption of DCTs and technology in clinical trials. For selected evidence projects, we collaborate with the BASE lab at Duke University (Duke), The Tufts Center for the Study of Drug Development (CSDD), and the Multi-Regional Clinical Trials Center at Harvard University (MRCT). In addition, Medable is an active member of many multi-stakeholder collaborations, such as the Clinical Trials Transformation Initiative, eCOA Consortium, the Avoca Quality Consortium, Society for Clinical Research Sites, Duke-Margolis ACT@POC, Decentralized Trials & Research Alliance, and the Pistoia Alliance – all driving understanding and improvements in clinical trials.

Medable appreciates the opportunity to comment on three aspects of developing and maintaining an infrastructure for emergency clinical trials outlined within this RFI document: Governance, Use of Decentralized Elements and Other Innovative Approaches for Clinical Trials, and Diversity Considerations.

The government plays an important role in implementing incentives and policies to facilitate the use of innovative clinical trial approaches in a Public Health Emergency (PHE) situation

and can use the warm research network to ensure best practices are tested and followed for inclusive and efficient trials.

Governance

A strong governance structure is critical to an effective clinical research infrastructure for emergency clinical trials. It allows for proactive planning and coordination, as well as the development of basic infrastructure that can be activated quickly in a PHE. The Office of Science and Technology Policy (OSTP) has identified several important issues that fall under governance, among which include thoughtful protocol development.

Clinical trials should be designed with a Quality-by-Design approach[1] upfront, with “quality” originally defined by CTTI, and adopted into ICH E8, as[2] “the absence of errors that matter to decision-making—that is, errors which have a meaningful impact on the safety of trial participants or the credibility of the results (and thereby the care of future patients)." Quality-by-Design approaches are critical for matching the capacity of clinicians taking care of patients during a PHE with the opportunity to participate in clinical trials. This approach can also offer a more streamlined design and conduct of the trial, including the incorporation of technology-driven decentralized modules.

Additionally, an “adequately empowered trial” requires that the specified number of participants for the analysis are actually enrolled and that participants complete their participation in the trial. An FDA evaluation of therapeutic clinical trials during the COVID pandemic showed that only approximately 5% of the arms of global clinical trials would be able to yield such reliable results as part of randomized and adequately powered clinical trials. Enrollment and retention of trial participants has been a critical issue in clinical trials, with issues mainly clustered in two buckets: burden of participation and awareness and access to clinical trials.

Observations from COVID, as well as previous extensive Public-Private Partnership experience from Medable executives responding to this RFI, offer a perspective that would benefit consideration in governance of a clinical research infrastructure:

- **Partnership among private and public organizations are critical and viewed as a key success factor during the COVID response[3].** Therefore, we recommend that the

[1] https://link.springer.com/article/10.1007/s43441-022-00454-5
[2] Meeker-O'Connell A, Glessner C, Behm M, Mulinde J, Roach N, Sweeney F, Tenaerts P, Landray MJ. Enhancing clinical evidence by proactively building quality into clinical trials. Clin Trials. 2016 Aug;13(4):439-44. doi: 10.1177/1740774516643491. Epub 2016 Apr 20. PMID: 27098014; PMCID: PMC4952025. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4952025/
[3] https://milkeninstitute.org/sites/default/files/2020-12/Silver-Linings_Executive-Summary.pdf

private sector be part of governance and that the private sector be represented by a variety of perspectives, such as drug and vaccine development (pharmaceutical, biotech and diagnostics) and trial infrastructure technology companies, as well as community-based health care organizations, such as retail pharmacies. Patient Advocacy Organizations and community-based groups serving underserved populations should also be represented.

- **Existing partnerships should be leveraged.** Early during the COVID pandemic, the government was able to leverage existing relationships to quickly communicate and coordinate with research stakeholders. As an example, the Reagan-Udall Foundation (RUF) hosted the COVID-19 Evidence Accelerator, which, through a collaborative approach, advanced the use of real-world data to inform our nation's pandemic response. We recommend consideration for the upfront use of affiliated organizations, such as the RUF, into a PHE as part of the governance model.
- **Barriers should be removed quickly to put trials into place.** We applaud OSTP for identifying the contracting and protocol development processes as barriers during the COVID PHE and addressing them through this RFI. We encourage consideration regarding which barriers were removed during the PHE and how those adjustments can be continued for ongoing trials and throughout the warm research system. Lessons learned for successful strategies to reduce and eliminate barriers should be incorporated into governance documents before the next PHE.

Use of Decentralized Elements and Other Innovative Approaches

As defined in the Food and Drug Omnibus Reform Act of 2022 (FDORA[4]), a DCT is a "clinical study in which some, or all, of the study-related activities occur at a location separate from the investigator's location". DCT configurations should be fit-for-purpose and based on the study populations, conditions under study, and the phase of development. The overarching goal is to improve participants' access and experience while maintaining their safety, improving the site experience, maintaining/improving data quality, and increasing study performance (measured in metrics of cycle times, improved diversity, and reduced cost).

The National Academies of Medicine proceedings report[5] of the virtual clinical trials challenges and opportunities referenced a Deloitte report that 70% of the US population lives greater than two hours from a clinical trial site. During COVID, many "hotspots" were

[4]https://www.congress.gov/bill/117th-congress/house-bill/2617/text&sa=D&source=docs&ust=1674769106184070&usg=AOvVaw0ddkC5nAnyzH1JCNz32Wpq

[5] *Read "virtual clinical trials: Challenges and opportunities: Proceedings of a workshop" at nap.edu*. Front Matter | Virtual Clinical Trials: Challenges and Opportunities: Proceedings of a Workshop |The National Academies Press. (n.d.). Retrieved January 26, 2023, from https://nap.nationalacademies.org/read/25502/chapter/1

located outside of the clinical trial centers and surrounding areas, with the normal travel burden being further compounded by restrictions and transmission concerns. Through the appropriate use of technology and decentralization, the DCT model provides an alternative to the traditional brick-and-mortar model, allowing participants to engage in research from the convenience of their homes via phone, computer, or within their community via local healthcare providers, such as retail pharmacies, local laboratories, and imaging centers.

Data collected in a DCT model can also be more comprehensive, passive and continual via the use of sensors, compared with the intermittent data collection conducted at a specific clinical trial site. This may be active collection of data or passive collection of data, decreasing the burden on participation and opening trials to people who previously were unable to participate or continue participation. Decentralized platforms enable all the technology and data to flow through one system, versus “stitching” different platforms together for connected sensors, eCOA collection and (e)consent. Simplicity can be observed with Single Sign On (SSO) for all participants, sites and sponsors and should include salient dashboards for each of the user groups.

Medable has supported research by the Tufts University CSDD*, which found substantial benefits in the use of DCTs in drug development. A first-of-its-kind evaluation[6] demonstrated that the typical DCT deployment for a clinical trial results in a one to three-month cycle time improvement (protocol development through database lock), yielding a net benefit that is up to five times greater than the upfront investment required for phase II and 13 times greater for phase III studies.

These benefits could make a significant impact during a future PHE scenario, as DCT efficiencies that result in trials completing earlier may provide answers that could be available one to three months earlier, potentially resulting in many lives saved. According to the CDC, mortality[7] from SARS-COV-2 was 384,536 in 2020 and 460,513 in 2021. Earlier randomized clinical trials with positive results for certain treatments, or trials that indicated a detrimental treatment, could have averted a substantial number of deaths.

During the COVID pandemic, innovative approaches were required to transition existing clinical trials (e.g. oncology trials where a clinical trial provides a care option), as well as begin new clinical trials to evaluate COVID diagnostic, vaccine and treatment options. As a company that has matured over the past 5 years and during the evolution of the pandemic,

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[6] DiMasi, J.A., Smith, Z., Oakley-Girvan, I. *et al.* Assessing the Financial Value of Decentralized Clinical Trials. *Ther Innov Regul Sci* (2022). https://doi.org/10.1007/s43441-022-00454-5

[7] https://www.cdc.gov/mmwr/volumes/71/wr/mm7117e1.htm#T1_down. Accessed Jan 17 2023

our experience has taught us the value that expanded use of decentralized approaches has on clinical trials through mechanisms such as eConsent, eCOA and telehealth.

Additional lessons learned highlight challenges, such as inequitable access to the internet and concerns around in-home visits. These systemic issues have to be addressed to fully capitalize on the benefits provided with increased use of technology and other innovative approaches. Actions need to be taken now to address access to broadband, internet and other technological barriers, especially as the healthcare infrastructure itself is increasingly reliant upon connectivity to provide care to patients. Please refer to the diversity section below for additional recommendations.

Specific suggestions for a emergency clinical trials infrastructure fall within several categories, including the following:

- **Privacy**. The FDA has been working with European Medicines Agency (EMA) (and others) on updating policies related to the use of decentralized approaches in clinical trials to ensure they are aligned with other aspects of trial design and execution; however, to facilitate the use of innovative approaches, there are some more general policies, specifically regarding privacy, that could greatly facilitate the use of decentralized approaches. The GDPR has become a de facto privacy policy floor for trials that have European sites. Given that clinical trials are often global and there is an established need for global cooperation during a PHE, it would be valuable for the US to review and consider a national privacy and security policy, minimally related to personal data processing for clinical research, that is aligned with GDPR to the extent feasible. This will facilitate technology solutions that do not have to be customized for state-by-state standards and, instead, have closer alignment to other countries in global trials.
- **Broadband and Internet access.** Policy discussions on internet availability have been ongoing. As technology solutions (such as connected sensors/apps to collect health data, and telemedicine visits) are becoming more common in clinical practice and clinical trials, the implications of unequal access to the broadband and internet infrastructure for public health should be part of policy discussions.
  Highlighting this inequity, there is a strong need for a national strategy that builds upon legislative efforts such as the “Data Mapping to Save Moms’ Lives Act”[8]. In this example, the proposed legislation would require the Federal Communications Commission (FCC) to identify areas where high rates of poor maternal health outcomes overlap with lack of access to broadband services so as to pinpoint where telehealth services can be most effective. With telemedicine becoming an integral part of delivering healthcare, as well as clinical trials, to the patients regardless of where a patient lives,

[8]https://www.congress.gov/bill/117th-congress/house-bill/1218

broadband infrastructure is as critical for better healthcare overall as it is for clinical trials. While 75% of adults in the US reportedly get internet access[9], broadband speeds[10] and costs[11] vary greatly across geography and income levels etc., potentially widening the chasm between the digitally-enabled and underserved populations.

- **Medical licensing and pharmacy licensing**. With the clinical trials enterprise moving away from localized efforts of "clinical trial deployments one research site at a time", the general concept of where data are collected is changing. Participants may be across state lines, and, in a decentralized model, that affects the ability to practice medicine and, therefore, the ability to conduct telemedicine visits for clinical trial purposes. We propose that, specifically in PHE clinical trials situations, an exemption be granted for the state medical licensing requirements as they relate to clinical trial activities. As a precedent, the Veterans Administration (VA)[12] has shown that a very large system with a state medical license exemption has been able to deliver quality care to veterans regardless of where the physician is located and licensed or where the patient resides. We recommend this model be expanded to any PHE situation so that trials can be deployed faster to states that may not have as many traditional clinical trial sites. The Interstate Medical Licensure Compact is an agreement among participating US states to work together to significantly streamline the licensing process for physicians who want to practice in multiple states. It offers a voluntary, expedited pathway to licensure for physicians who qualify and may be a foundation for a clinical trial exemption.
  To maximize trial participation, a PHE research license should be in conjunction with the use of telemedicine and DCTs. Even with the promising approach of clinical trials at point-of-care, especially in the early phases of a pandemic, people in remote areas may be left out. There could be momentum to build on the interstate Telemedicine compact[13].
- **Research and demonstration projects** on decentralized clinical trial methodologies and best practices in advance of the PHE. Now is the time to understand how DCT modules and elements impact the conduct of clinical trials so we can proactively optimize their deployment in a fit-for-purpose and evidence-based manner in preparation for the next PHE. By establishing an evidence-based approach to the deployment of studies, we enhance the ability to identify necessary treatments by focusing on studies that demonstrate improved efficiencies and make informed decisions to deprioritize/minimize

[9] https://www.pewresearch.org/internet/fact-sheet/internet-broadband/#panel-9a15d0d3-3bff-4e9e-a329-6e328bc7bcce
[10] https://www.theverge.com/22418074/broadband-gap-america-map-county-microsoft-data
[11] https://www.theverge.com/2022/11/17/23460070/internet-bill-broadband-survey-data-consumer-reports-cost
[12] https://www.hsrd.research.va.gov/news/feature/telehealth-1122.cfm
[13] http://www.imlcc.org/

trials that cannot deliver results. While Medable is committed to operating with these types of activities, a broader, government-funded effort can have a greater impact.

- **Minimize patient and site burdens** and increase their flexibility. The power of decentralization is that it allows greater flexibility for participants and sites with respect to driving enrollment as well as retention. Establishing statistically significant results begins with enrollment, as this is critical to answer the research questions around treatments postulated in clinical trials. The criticality of getting an adequately-enrolled trial is never more true than during the emergence of a pandemic, when speed is of the essence and the price of poor data is lives lost. A better understanding of the issues and opportunities for improvement surrounding patient enrollment and patient and site burden can be gained through the proposed research mechanisms described above as well as through a public solicitation for comments. Organizations, such as SCRS and the Association of Clinical Research Professionals (ACRP), have great insights on these issues.

Diversity Considerations

If we, as a society, have learned anything over the past few years, it is the overwhelming importance of diversity in healthcare (as it is in every aspect of life). Patients in clinical trials need to reflect the population living with the condition, with a mindfulness of diversity with respect to race and ethnicity, rural versus urban, gender, age, and other factors. Traditional brick-and-mortar trials have fallen short of that ideal, with the most recent 2021 FDA snapshot[14] data showing a gap between the trial populations enrolled and the US census. On a positive note, there is significant momentum from federal agencies (FDA, NIH, etc.) as well as legislative action (DEPICT Act passed in the late 2022 Omnibus) in support of expanding access and diversity in clinical research. Specifically, the DEPICT Act requires that study sponsors provide a detailed diversity action plan in their proposed study protocol. For decades, studies have not included adequate representation of minority populations, neither as a function of the US population overall, nor as a reflection of the populations bearing the highest burden of disease for a given indication. Tools, such as DCT platforms, enable rapid access to clinical studies for potential participants who may otherwise not be able to access them. This is a critical enabler for sponsors to recruit and retain participants from varied geographic, cultural, ethnic, age, and educational backgrounds. Using technology enables potential and actual trial participants to engage in clinical research, reducing the limitations of physical proximity. It also allows for customized approaches to maximize recruitment, participant satisfaction, and retention based on the targeted trial populations' specific needs. For example, the technology interface for a teenage pediatric participant population may vary significantly from that of an elderly participant population living in a rural community. Technology, in partnership with sponsors, community organizations, government, and other stakeholders, is needed to achieve true diversity.

[14] https://www.fda.gov/media/158482/download

Depending on the type of diversity sought, different partnerships may be required to optimally engage a certain community. Achievement of racial and ethnic diversity may require different strategies than achievement of gender, age, or economic/geographic diversity, so specific cultural, regional, and community mindfulness must be considered when preparing to engage and enroll these patients.

Several DCT modalities, such as “bring your own device” (BYOD), are key elements allowing for the democratization of access to clinical studies. Additionally, patients may participate within their communities, engaging with physicians whom they already have established care, and performing routine clinical assessments from their homes or places of work. These new approaches toward enabling access to clinical trials have gained widespread acceptance, not only by study sponsors, but also by global regulatory bodies. The US FDA is expected to release its DCT guidance document in the near future, which has been developed and harmonized with the EMA recommendations document released in December 2022.

Specific suggestions for increasing diversity of clinical trial participants within a national clinical trials infrastructure for PHEs include the following:

- Conduct a national assessment and plan for increasing diversity during a PHE, building upon the COVID vaccine trial efforts and other frameworks that are emerging.
- Support pilot projects to evaluate aspects of the plan in the context of “warm research,” to include partnerships with organizations in large geographic areas of underserved populations. As an example, one study design may evaluate, in a randomized approach, the diversity methodologies and models in clinical trials run in the warm disease network. Incorporating innovative approaches, such as decentralized elements, and using local providers within pilot projects also enhances this recommendation.
- Consider opportunities to build upon, and engage with, existing government programs (e.g. VA, NIH networks) and public-private partnerships (e.g. CTTI) which have efforts to increase diversity in clinical research.

Dr. Arati Prabhakar
Office of Science and Technology Policy
Executive Office of the President
Eisenhower Executive Office Building
1650 Pennsylvania Avenue
Washington, D.C. 20504

December 27, 2022

Re: October 26, 2022, Emergency Clinical Trials RFI

Dear Dr. Prabhakar,

Thank you for the opportunity to submit comments on behalf of Weill Cornell Medicine|NewYork Presbyterian's Joint Clinical Trials Office (JCTO). The JCTO was established in 2013 to provide the infrastructure for excellence and efficiency in clinical research, with the goal of increasing the volume, quality, and impact of clinical trials at our institution. The JCTO provides foundational support for designing, initiating, and conducting clinical trials for a range of diseases. It helps investigators at Weill Cornell Medicine and NewYork Presbyterian answer important scientific questions by providing assistance in designing and initiating trials and connecting them with patients who generously volunteer as study participants. Through the JCTO, patients can learn about available clinical trials at Weill Cornell Medicine and NewYork Presbyterian and across our institutional network in Manhattan, Brooklyn, Queens and Westchester.

As the Director of the JCTO, I would like to provide the below comments in regard to a few prompts from the October 26, 2022, Emergency Clinical Trials Request for Information (RFI). These comments are illustrative of the JCTO experience during the COVID-19 pandemic and not intended to be exhaustive.

If you have any questions or would like further information on anything described herein, please contact Weill Cornell Medicine's Associate Director of Federal Relations Alessia Daniele at ald2035@med.cornell.edu or by phone at 914-552-3818.

Sincerely,

Mario Gaudino, MD, PhD, MSCE
Stephen and Suzanne Weiss Professor in Cardiothoracic Surgery (II)
Assistant Dean for Clinical Trials
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Request for Information; Clinical Research Infrastructure and Emergency Clinical Trials

1. ***Governance for emergency clinical trials response.***

e. Mechanisms for tracking institutions, networks and sites that might be able to participate in emergency research, to ensure adequate potential for enrollment and adequate geographic coverage, domestically and internationally.

The ROMA trial, a large-scale, multi-center, international surgical trial including over 70 international centers, has informed our experience in clinical trial management during a global pandemic. The ROMA trial has been able to maintain consistent enrollment during the global pandemic (see figure below) while many clinical trials and research were discontinued entirely. While there are many reasons for the consistency of enrollment in ROMA, one particularly salient point is its geographic distribution. ROMA was a truly global trial, with multiple sites not only in different countries, but also in different continents. The COVID-19 pandemic reached its crescendo in different parts of the globe at different times; for example, while European enrollment may have decreased at the peak of the pandemic in that continent, American and Asian enrollment continued. This pattern has been repeated over the course of the pandemic to allow for steady and consistent enrollment over time. The importance of having a truly global trial infrastructure in order to facilitate continued recruitment cannot be overstated.

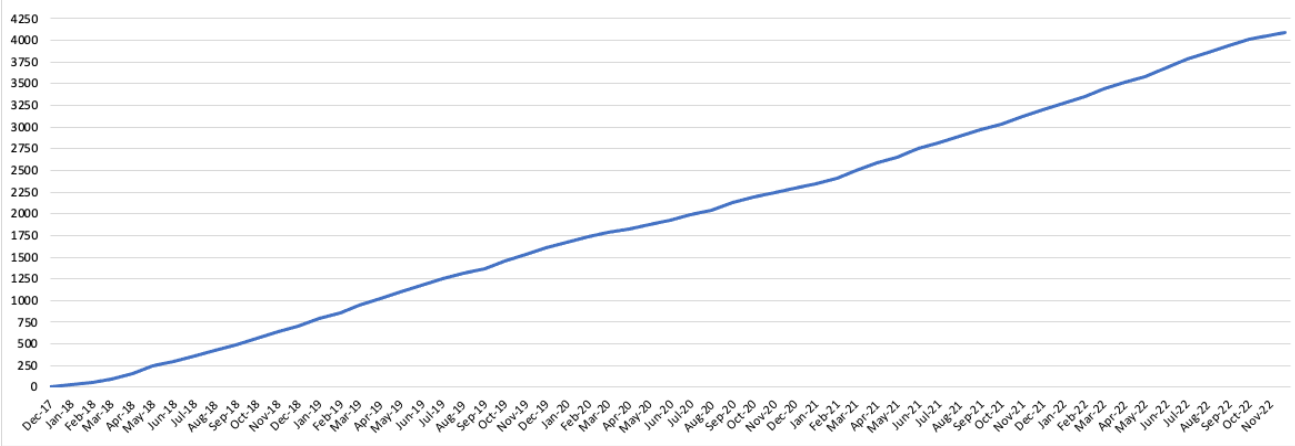

Figure 1. *ROMA cumulative enrollment.*

j. Appropriate entities to handle projecting and tracking enrollment at study sites, monitoring the progress of clinical trials, and data management; whether existing entities could be engaged or adapted to carry out these functions for coordinated, large-scale emergency clinical trials.

All global clinical trial networks should remain active for increased adaptability and so that trial apparatus can be repurposed quickly if necessary. When there is constant communication and trial activity, even if the activity is low-grade, the trial remains able to rapidly change and grow. In addition, if personnel and protocols are seasoned in trial organization and management, they can adapt to provide greater assistance as needed in the face of emergency.

If an existing international trial falls dormant at any point, i.e., if activity and communication ceases, the trial has become inadaptable. Administrative bottlenecking can occur for myriad reasons: loss of point of contact, personnel changes, loss/lack of knowledge of protocol implementation, and so forth. Trial networks must be kept in tune with routine activity such that when a catastrophe strikes, activity can be ramped up quickly and efficiently to meet the new challenge in lieu of wasting valuable time making rusty trial apparatus functional once again.

6. International coordination and capacity.

c. Overcoming regulatory barriers that delay expansion of U.S. trials into international sites, or otherwise interfere with clinical research across borders.

Please see our full comments on item 1-j, which are applicable to this question. In brief, in order to avoid bureaucratic or administrative delays at critical moments when speed and efficiency are of utmost importance, existing clinical trial networks must remain consistently in use so that trial personnel have the understanding and ability of how to rapidly manage these items and avoid costly delays.

In addition, our experience with the ROMA trial has demonstrated that the willingness of international sites to participate is related to the cost and simplicity of the intervention. The intervention of the ROMA trial can be performed in a way that minimizes any disruption to routine operating room procedure and does not require any change or increase in clinical personnel or clinical capacity. The requirement for any in-person research personnel is similarly minimal. The ease of implementation has led to widespread participation and has also allowed for the trial to continue in the face of personnel and supply-chain shortages occurring throughout the pandemic. These comments may also be applicable to prompt 6-a regarding designing the overall domestic emergency clinical trials effort in a way that coordinates with international clinical research efforts.

American College of Emergency Physicians (ACEP) and the Society for Academic Emergency Medicine (SAEM) Joint Statement on Research During the COVID-19 Pandemic

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As with environmental disasters and other crisis events, pandemics often present challenges within and beyond the clinical environment. Pandemics significantly impact medical research through decreased effort available for research due to necessary clinical duties, quarantined staff, disrupted research infrastructure and protocols, closed sites, limited travel, and confounding introduced by infection of trial subjects, as well as changes in the standard practices within the healthcare system. Given the uncertain duration of this pandemic, researchers should be prepared to introduce modifications to the conduct of research that will aid in the safe conduct and efficient completion of emergency medicine research in the current practice environment.

Emergency medicine is on the front line of pandemics, and emergency medicine investigators are uniquely positioned to study undifferentiated patients with symptoms consistent with COVID-19, patients diagnosed with COVID-19, and other related domains. In the spirit of disseminating best practices, and to provide a consensus on the conduct of emergency medicine research, the American College of Emergency Physicians (ACEP) and the Society for Academic Emergency Medicine (SAEM) together make the following recommendations:

Investigators should:

- Continue to adhere, to the greatest extent possible, to the principles of scientific and methodological rigor for new and existing projects
- Collaborate with other acute care researchers and professional societies to ensure the timely implementation of research supporting the efforts of frontline providers, including:
    - Rapid development and implementation of hypothesis-driven observational studies related to the COVID-19 pandemic, including diagnostic, therapeutic, and prognostic outcomes.
    - Rapid development and implementation of scientifically-sound and methodologically rigorous clinical trials related to COVID-19, with emphasis on quick turnaround and adaptive designs.
    - Development of a targeted COVID-19 research agenda that addresses issues such as timely identification and interventions, prioritization of study drugs/ intervention, coordination of study resources, and the use of central IRB review and approval of study protocols.
    - Development of research platforms, standard operating procedures, and consortiums to be deployed in the event of future pandemics, crises, or national emergencies.
- Consider social determinants of health, while engaging and involving the broader community in the implementation of any treatments or interventions
- Work closely with their institutional review board (IRB) and other regulatory bodies to facilitate rapid protocol review / revision / adaptation / contract review on COVID-19 related studies.
- Develop mechanisms to ensure that pre-existing clinical research protocols can be completed with as little disruption as possible to the plan outlined in the existing protocol.
- When feasible and appropriate, inform previously enrolled study participants of any changes to pre-existing research protocols that may result from the COVID-19 pandemic, including updated subject safety procedures, changes to study design or any other anticipated disruption of the management plan outlined in the original protocol.

- Consider use of Exception For Informed Consent (EFIC) and Waiver of Informed Consent (WIC) techniques where applicable to facilitate time-sensitive, potentially life-saving treatment; or when legally authorized representatives for critically ill patients are unable to provide consent or cannot be contacted in time due to infection control policy in place.
- Reduce potential infectious exposure for study team members and conserve personal protective equipment (PPE) by utilizing electronic, video or telephonic consenting / interviewing / monitoring techniques, minimizing in-person interactions between subjects and study team members, utilizing minimal specimen procurement and drug administration strategies and utilizing electronic and telehealth for follow-up monitoring.
- Current animal-based research not associated with the COVID-19 outbreak should be managed responsibly and humanely. As feasible, research should continue with appropriate social distancing in the laboratory setting as well as limiting workers to essential functions/experiments.

Departmental Research Administration should:

- When feasible and appropriate, support junior and early career researchers by creating alternative opportunities to large scale funded clinical trials (e.g., observation cohort studies, retrospective studies on collected data, open sharing of de-identified patient-level data, small pragmatic trials, involvement in data analysis and manuscript preparations, teaching and disseminating knowledge online).
- Provide resources and equipment for remote work to research staff if applicable.
- Develop strategies to keep research staff employed by either performing research activities (e.g., supporting COVID-19 research, working on existing research projects remotely), or being redeployed to clinical or clinical support roles.
- Facilitate interdisciplinary and interprofessional research opportunities that incorporate all aspects of emergency care (e.g., pre-hospital, emergency department, telehealth).

Grantors of research funding should:

- Consider deadline extension for grant applications, or provide assistance in obtaining no-cost extensions, in line with NIH practice.
- Support junior and early-career emergency medicine researchers by providing funding opportunities for funding of observational cohort studies, retrospective studies on collected data, small pragmatic trials, and other alternatives to large-scale prospective clinical trials.
- Centrally coordinates between sites and networks to capitalize on research efforts.

Institutional Offices supporting research should:

- Develop standing contingency plans that can be activated in times of pandemics, national emergencies, or other crisis events (e.g., remote functioning of the IRB, access and pathways to data, follow-up plan for previously enrolled patients, methods to safeguard subject privacy/ confidentiality during remote operations, structured plan for halting and re-starting recruitment).
- Develop financial continuity plans for emergencies that enable investigators to maintain external funding support for work performed remotely or otherwise modified to be performed under changing clinical conditions.
- Work to expedite review and approval of research proposals relating to COVID-19, understanding the fast-moving pace of this pandemic.

- Centrally coordinates trials across networks to prevent duplication of efforts, maximize startup activity and leverage bandwidth across institutions.

Professional Organizations, including associations of healthcare workers and peer-reviewed journals that publish medical reports, should:

- Facilitate the efficient dissemination of knowledge gained. Examples include late-breaking submission for scientific conferences, virtual presentations, and fast-track peer-reviewed journal publications of COVID-19 related research.

Additional Resources:

- Council on Governmental Relations (COGR) - Institutional and Agency Responses to COVID-19 and Additional Resources
- National Institutes of Health (NIH) COVID-19 guidance

Contributors: Samuel Lam, Alex Limkakeng, Bernard P. Chang, Joshua Davis, Sangil Lee, Nidhi Garg, Rob Ehrman, Michael Gottlieb, Anna Marie Chang, Layne Dylla, Anthony Thomas Lagina, Muhammad Waseem, Joseph Miller, James H. Paxton, Charles B. Cairns, Justin Belsky, Loren Rives, John T. Finnell

Clinical Research Infrastructure and Emergency Clinical Trials

Response to the White House Office of Science and Technology Policy

Oracle America, Inc.

Document Number: 2022-23110 | January 27, 2023 | 5:00 PM (ET)

This submission is provided for informational purposes only and is not an offer to enter into a contract of any kind with the US Government.

Submitted to:
White House Office of Science and Technology Policy
Executive Office of the President
Eisenhower Executive Office Building
1650 Pennsylvania Avenue
Washington, D.C. 20504
Attention: Grail Sipes, Assistant Director

Submitted by:
Oracle America, Inc.
500 Oracle Parkway
Redwood Shores, CA 94065
Jerrold Johnson, Applications Sales Representative

Oracle America, Inc.

500 Oracle Parkway
Redwood Shores, CA 94065

January 27, 2023

Grail Sipes, Assistant Director
White House Office of Science and Technology Policy
Executive Office of the President
Eisenhower Executive Office Building
1650 Pennsylvania Avenue
Washington, D.C. 20504

Dear Ms. Sipes:

On behalf of Oracle America, Inc. (Oracle), thank you for the opportunity to respond to the White House Office of Science and Technology Policy (OSTP). Oracle is providing comments to address the Clinical Research Infrastructure and Emergency Clinical Trials Request for Information (RFI).

Our response explains how Oracle can help. Indeed, since 1977, we have helped hundreds of thousands of customers of all sizes around the globe simplify their processes by engineering hardware and software to work together. We drive transformation inside the health industry with dedicated vertical organizations with deep domain industry expertise to provide best-of-breed technologies to help solve the most complex business problems.

Oracle offers a complete technology stack in the cloud, on premise, and in the data center. Our portfolio of products gives customers complete deployment flexibility and the unmatched benefits of application integration, powerful performance, high availability, scalability, advanced security, energy efficiency, and low total cost of ownership. We help develop strategic, efficient processes by adopting technologies that enable healthcare and life sciences organizations to provide reliable, secure, and scalable technologies and processes that deliver results for their customers.

In fact, Oracle's cloud products help businesses, health sciences companies, and public institutions modernize, innovate, and compete in today's digital world. With this modern cloud, OSTP can meet your organization's objectives more quickly and efficiently.

In addition, we not only provide robust products, but Oracle also works with you on every step of the digital journey. OSTP will benefit from Oracle's customer support services and can also take advantage of optional services, such as consulting, training, upgrade support, and financing. We will help you get the most out of your Oracle products so that you can meet your business objectives.

We value our growing relationship with OSTP and are excited to enhance it. Please feel free to contact me if you have any questions or would like further information. I can be reached at +1.443.756.8641 or via email at jerrold.johnson@oracle.com.

Sincerely,

DocuSigned by:
Jerrold Johnson
5D08FE03C9DF41B...

Jerrold Johnson
Applications Sales Representative

Table of Contents

Response Guidelines

Corporate Entity

This response is being made by Oracle America, Inc., a wholly owned subsidiary of Oracle Corporation. All responses reflect information concerning Oracle Corporation (hereinafter referred to as Oracle) except where otherwise indicated as being information of Oracle America, Inc. (hereinafter Oracle).

Understanding Oracle Terminology

Oracle understands the task ahead for OSTP to review and compare responses for your project. We believe both you and Oracle benefit from a common understanding of terminology. We have included "Appendix A: Definitions and Abbreviations Used in Oracle's Response." Please refer to this appendix for further details about what you can expect from Oracle should we win your business.

Response Validity

This Response shall remain valid until May 31, 2023, unless otherwise mutually agreed, in writing, by Oracle and OSTP.

Executive Summary

The COVID-19 pandemic revealed gaps in the national coordination of research and development activities needed to design effective public health measures and prevent severe disease. However, the COVID-19 pandemic also served as a catalyst for imagining and deploying new ways of monitoring public health, accelerating drug development, and administering and monitoring newly developed diagnostics, therapeutics, and vaccines. Oracle has proactively developed infrastructure, tools, and services that can address many of the gaps highlighted by the White House Office of Science and Technology Policy (OSTP) and accelerate coordination of complex multi-site clinical trials in emergency and non-emergency conditions. Through collaboration with OSTP and other partners, Oracle looks forward to continuing to innovate improvements in future clinical trial research and development activities. Oracle's direct experience creating software tools and services designed to enhance coordination and expedite the conduct of clinical trials includes the following:

- A learning health network (LHN) is a diverse, nationwide network of more than 100 healthcare provider organizations that share data for rapid research activation. Research consortiums like the Oracle LHN, which are established and actively participating in research activities, may be utilized by OSTP to rapidly enable "warm base" research activities.
- A Real-World Data (RWD) infrastructure to expedite cohort discovery and increase efficiency in research activities. Oracle's RWD leverages de-identified data from our LHN consortia members that may be used to expedite evaluation of study feasibility and is an invaluable resource for efficient trial design.
- Software tools, both within and outside the electronic health record (EHR), to rapidly activate and scale clinical research activities. Integrated clinical trial management software provides avenues to coordinate, standardize, and scale complex protocols across geographies and care settings.

The tools and services described above inform the recommendations contained herein that are offered to assist OSTP and the research community to strengthen the current national clinical trial infrastructure.

Topic 1: Governance for emergency clinical trials response.

a. Models that could be used to establish a U.S.-level governance structure for emergency clinical trials.

OSTP may wish to consider incorporating elements of Australia's national clinical trial framework, the only nation with published guidance in this area. For critical public health and safety issues, Australia's centralized model expedites clinical trials while maintaining appropriate participant protections[1]. While this framework will be useful when developing a U.S.-led governance structure, a broader coalition will be needed to represent U.S.-based and international stakeholders. In addition to including the traditional public health stakeholders (public health researchers, clinicians, patient advocates) in this governance infrastructure, technology providers at the intersection of clinical research and patient care will be fundamental in operationalizing the infrastructure and should be included in governance structures to advance practical implementation of recommendations.

b. Criteria to determine when coordinated and potentially large-scale clinical research is needed.

Initiation of emergency clinical research should be linked to the same criteria to declare a public health emergency to avoid unnecessary redundancy (which includes but is not limited to: R0 value, the average number of disease cases that arise from a single infected person; death rate/projected mortality rate, the estimated number of deaths in a population divided by the total population; geographic coverage, where the disease has been detected and likelihood of spread to other areas; and reinfection status). Linking emergency clinical trial activation to these criteria will ensure expeditious movement to understand the disease, inform public health recommendations, and work toward effective treatments and therapies.

c. Outbreak or incident factors to consider in determining what types of studies are needed.

After determining the need for emergency research, observational *and* interventional studies should be initiated to better understand the disease and to develop effective treatments and therapies for prevention, harm

[1] https://www.safetyandquality.gov.au/our-work/clinical-governance/national-model-clinical-governance-framework

reduction, and treatment. Factors that should be considered for observational studies include comorbidities (including health status and diagnoses that influence disease severity), mode of transmission (including the best methods to protect against spread), infectivity, environmental factors, local policy measures or mandates that influence disease epidemiology, disease type, the development time horizon for treatment, and harm (mortality/morbidity) reduction through medication.

d. Methods for communicating emergency clinical research decision.

OSTP may wish to consider capitalizing on the ability of health technology companies (such as those who interface with healthcare facilities and provide clinical trial software and services) to communicate the directive to initiate emergency clinical trial research *and* begin the process to implement study start up protocols rapidly. Technology providers have wide-ranging relationships at healthcare organizations, including system administrators, providers, researchers, business office/accounting, and technology staff. These existing relationships provide an effective springboard for rapid mobilization of clinical trial activities, particularly in circumstances where healthcare technology providers facilitate and support networks that promote and accelerate research. Advantages associated with using healthcare technology providers include reaching appropriate healthcare facility stakeholders, rapidly integrating clinical trial protocols to the existing technology stack, standardizing the protocol across various institutions, and implementing study startup at scale by leveraging existing agreements and data sharing networks.

e. Mechanisms for tracking institutions, networks and sites to participate in emergency research.

Oracle recommends leveraging existing networks of healthcare institutions to enable the tracking and rapid recruitment of sites for emergency clinical trials and implementation of approved protocols. For example, Oracle has a large network of healthcare clients covering 100 million patients across the U.S. designed for rapid research activation. The network federates data into a single database that may be used to expedite and enable multi-site clinical research. Our geographically disperse and demographically diverse network may be leveraged to enable emergency research and ensure adequate participant enrollment for studies within the U.S. Should OSTP proceed with the program described in the RFI, this model could also be expanded to international clients that use the Oracle EHR.

i. Criteria to establish a target number and location of sites to support emergency clinical trials.

Oracle recommends that clinical trial sites for this program be reviewed for the following criteria:

- **Demographic diversity** (demographics of potential participants compared to the most recent U.S. census)
- **Geographic diversity** (nationally and/or internationally if applicable to the public health emergency)
- **Urban/rural diversity** (various community types, nationally and internationally, if appliable)
- **Healthcare facility diversity** (including critical access, ambulatory, long term care facilities)

f. Procedures to oversee development of clinical trial protocols and investigational agent selection.

Currently, clinical trial protocol development is the responsibility of the research study team, which often includes a medical expert, statistician, pharmacokinetics expert, clinical research coordinator, and project manager. Studies begin after the study sponsor submits the protocol to the U.S. Food and Drug Administration (FDA) for review and the Institutional Review Board (IRB) approves the protocol. The National Institutes of Health (NIH) Office of Science Policy provides detailed templates to help research teams structure and organize critical elements of a clinical trial[2]. The NIH Institute of Allergy and Infectious Disease[3] provides the most detailed description of rules and regulations for the appropriate conduct of clinical trials. The U.S. Department of Health and Human Services (HHS) has a key role overseeing the agencies (including the Centers for Disease Control and Prevention [CDC], FDA, NIH) needed to coordinate activities for an emergency clinical trial response and is therefore best positioned to convene appropriate agency leaders, in conjunction with industry and academic stakeholders, to create the clinical trial protocol. Oracle recommends that healthcare research technology providers be included in the planning and development of this activity.

[2] https://grants.nih.gov/policy/clinical-trials/protocol-template.htm
[3] https://clinregs.niaid.nih.gov/

g. Best practices, including "quality by design" principles.

Quality by design principles for clinical research depend on the study type. For example, an interventional emergency clinical trial studying the safety or efficacy of an investigational drug or vaccine would have distinct quality by design characteristics from an observational trial seeking to understand the demographics or health characteristics of individuals more prone to severe disease. The quality by design principles for clinical trials should be determined based on study type rather than a universal set of principles that apply to all trials.

h. Best practices for designing trials that can enroll vulnerable populations, such as pediatrics.

OSTP should review the detailed HHS guidance[4] regarding protections for vulnerable populations (such as children, prisoners, and people with sexually transmitted infections) in clinical research. Additionally, local and state laws may need to be considered since they impact the process for outreach, recruitment, and enrollment. For example, the definition of a child or minor is not consistent in all states and localities. Current best practice is to staff a legal expert for a national study to advise on customization of consent protocols relevant to specific vulnerable populations and participant geography. In theory, many of these requirements could be automated based on discrete demographic rules built into clinical research recruitment tools.

i. Optimal ways to manage interactions with domestic and international regulatory bodies.

No comment.

j. Appropriate entities to handle projecting and tracking enrollment at study sites.

Existing organizations and solutions are available to manage these activities. Software solutions should integrate a CTMS with a robust EDC system designed for clinical trials (specifically to track study enrollment at study sites, monitor progress and regulatory compliance of clinical trials, manage data, and coordinate activities across decentralized study sites). Contract research organizations (CROs) can be used to coordinate site startup and oversee participant outreach, recruitment, and enrollment for large multi-site studies.

k. Structuring a data repository and a biorepository for emergency clinical trial data and specimens.

A reasonable precedent to guide the structure of these repositories is the NIH's *All of Us* program[5], which is a national longitudinal study aiming to enroll 1 million participants nationwide. For the **data repository**, the *All of Us* Research Workbench[6] houses in-depth health data, a powerful analytics platform, and a variety of tools to conduct a wide range of studies. The workbench has a rigorous approval process for a role-based access based on stakeholder need. We recommend implementing a similar role-based access on a cloud-based infrastructure that can maintain high security standards and privacy protections for sensitive patient data. For the **biorepository**, the *All of Us* biobank is a storage facility that stores and manages biological samples (including blood, urine, and saliva) for use in research. Oracle recommends that the clinical laboratory partner selected to support the biorepository for the work detailed in the RFI demonstrate a willingness to integrate with national EDC infrastructure for sample kit tracking and sample accessioning.

l. Criteria that should be applied to govern researchers' access to emergency clinical trial research data.

Oracle recommends OSTP consider three access tiers for clinical trial research data to provide an appropriate level of transparency for the public while also allowing researchers with specific permissions access to more robust data: **(1) Public tier**, which includes aggregate data with all identifiers removed and is made available via data browser. This tier may be used to keep the public informed of relevant activities related to the public health emergency. **(2) Registered tier**, which may contain individual-level data to be available only to approved researchers. This may include data from EHRs and other sources collected during emergency clinical trials. **(3) Controlled tier**, which may contain more detailed information critical for public health officials, data scientists, and researchers to evaluate to inform public policy and emergency response during the emergency. This approach is consistent with data controls implemented on several prior and ongoing national clinical trials sponsored by the U.S. federal government.

[4] https://www.hhs.gov/ohrp/regulations-and-policy/guidance/vulnerable-populations/index.html
[5] https://allofus.nih.gov/about
[6] https://www.researchallofus.org/data-tools/workbench/

Topic 2: Identify & Incentivize Networks; Build Diversity & Equity.

a. Identifying institutions and sites that are interested or familiar with emergency clinical trial research.

Existing healthcare research networks can provide OSTP access to many of the healthcare provider organizations across the United States for the emergency clinical trial program. Networks that are most able to participate in emergency clinical trial research will require existing data use agreements that permit aggregation of de-identified health information for use in retrospective research activities or as a basis for potential study recruitment among member organizations. For the work described in the RFI, it will also be helpful to have a network that includes vendor partners with capabilities to expedite clinical research activities for network members from multiple sites or facilities.

b. Effective ways to increase diversity and to expand clinical research sites into underserved areas.

i. Community outreach.

Typical models for community outreach engage specialized vendors to perform this activity as part of a concerted campaign to recruit a diverse, qualified pool of participants. Oracle recommends leveraging real-world data resources to prioritize geographies and/or specific health systems for outreach to facilitate recruitment of diverse and underrepresented populations in the research cohort.

ii. Use of decentralized clinical trial (DCT) design elements, or other innovative approaches.

Enabling remote interaction (with wearables and patient sensors) through DCT models can increase geographic diversity for patients and clinicians in clinical trials but requires appropriate equipment and internet access. DCTs also allow patient data (such as from wearables and patient sensors) to flow automatically into a central platform where it is available across all clinical trial processes, reducing redundancy and time-consuming tasks (such as data entry) typically found in centralized trials. By reducing redundant and time-consuming tasks, DCTs have the potential to increase clinical trial participation by smaller teams that may not have had previous capacity. Increasing the diversity of organizations participating in clinical trials can be furthered by partnering with vendors that provide clinical trial management solutions that integrate with the EHR by enabling research workflow standardization across participating institutions. Standardizing research workflows, especially at institutions that lack a large research staff, can enable the participation of small facilities (such as critical access hospitals, which are typically excluded from clinical trials due to capacity). This expands diversity and reach of clinical research activities for the healthcare organizations, Principal Investigators, and the patient populations that they serve. However, in practice, participating sites may not have the correct software or technology to enable modifications to workflows within the EHR. In these cases, it is best to engage a full service CRO or partner that will directly provide staffing and ensure protocol adherence at participating study sites.

iii. Use of technological innovations for remoteparticipation

Participant mobile health applications promote outreach, access, and participant diversity by alleviating geographic constraints for clinical trial participation. It is important that these applications facilitate the centralization of data (including health status data) to a common location to facilitate study objectives.

iv. Building on existing programs that target diversity in clinical research.

Published reports[7,8] detail various approaches to diversity and inclusion in outreach and highlight the importance of directed outreach to underrepresented communities and leveraging underrepresented providers during recruitment. The NIH *All of Us* program, for example, is one of the most successful examples that focuses on diversity in clinical research and currently has more than 500,000 U.S. participants. Separately, technology can also be used to help address outreach by facilitating rapid access to a large diverse patient population and prioritizing outreach to these groups.

v. Leveraging the networks and community access of retail chains, including retail pharmacy chains.

Retail chains have broad outreach capabilities compared to others in the healthcare research space. A multi-prong approach that uses both the retail chain's population access in addition to healthcare facility population

[7] https://pubmed.ncbi.nlm.nih.gov/32004412/
[8] https://www.nejm.org/doi/full/10.1056/NEJMsr1809937

access would maximize and speed inclusion of diverse participants into clinical trials. Established clinical research networks (such as those developed/supported by EMR vendors) enable more sophisticated clinical trial activities due to the inherent capabilities of healthcare service providers.

vi. Leveraging community-based care networks such as Practice-Based Research Networks (PBRNs) and Federally Qualified Health Centers (FQHCs).

Incorporating PBRNs, FQHCs, and other community-based care networks is an effective strategy to access broad patient populations for recruitment. Health IT vendors also retain large client networks with established governance and data use agreements that can accelerate participant outreach and recruitment.

c. Incentives that can encourage participation in emergency clinical trial research.

i. Creation of pilot program enabling clinical trial data collection across a wide variety of trial sites.

Research[9] suggests that financial incentives are the most effective to incentivize institutions and sites to participate in clinical research studies. A stable source of program research funding will also help facilities support and retain staff and Principal Investigators to perform clinical research.

d. Once interested institutions or networks are identified,

i. Effective ways to recognize & communicate commitment to emergency clinical research.

No comment

ii. Information that should be collected from interested sites (for example, from questionnaires).

Questionnaires will require healthcare facility staff to spend time finding and submitting the requested information and therefore may place an unintended burden on facilities wishing to participate in this type of program. Instead of a questionnaire, EHR providers may deliver a more reliable and expeditious method to provide site characteristics, including patient population and site personnel capabilities.

e. The best ways to provide training in clinical trial practice (including regulatory requirements such as GoodClinical Practice (GCP)).

Sites that wish to participate but may not have full capability to conduct a clinical trial may be trained or augmented by contract research partners experienced in providing study startup activities for site activation.

Topic 3: "Warm Base" Research

a Disease areas that should be targeted in protocols for "warm base" clinical research:

i. Disease areas that are most relevant to communities, including underserved communities.

Underserved communities would benefit from a focus on Type II diabetes, obesity, and cardiovascular disease (particularly hypertension and hypercholesterolemia). These are widespread issues, are costly to treat, and research as a care option could bring therapies to underserved communities.

ii. The extent to which "warm base" research should target infectious disease vs. other conditions.

OSTP may wish to consider additional “warm base” clinical trial opportunities including vaccine research for acute illness (such as, influenza, pneumonia) and oncology biomarkers (for example, blood screenings for cancer). The size of the network and patient population must be sufficient to show statistical significance for the specific protocol. As such, statisticians should be involved in protocol development to ensure adequate statistical power from the beginning of the clinical trial. For healthy patients who are screened for diagnostic studies at these sites, a patient registry may also be useful to have a “warm base” of patients qualified for certain trials. “Warm base” research would best be conducted within an established network of sites with experience running diverse trials in vaccine, virology, and oncology diagnostics.

b. How "warm base" research could best be implemented to provide training to inexperienced sites, and to create a basic level of surge capacity at the staff level for emergency clinical trial research.

We recommend that OSTP use a vendor/partner ecosystem to enable training for research-naïve sites and to provide surge capacity and staffing for emergency clinical trials. Vendors are available to assist with onboarding healthcare sites for clinical trials, including those with little research experience. Upon agreement to participate

[9] https://www.amjmedsci.org/article/S0002-9629(15)31157-5/fulltext

as a clinical research site, the vendor provides the site a core set of training, including Good Clinical Practices, and collects all critical documents. When a clinical research protocol is initiated at that site, the vendor also provides primary investigator and site personnel with study-specific training. Some vendors also provide contract staffing (including a flexible research coordinator pool) which may be able to provide surge capacity for emergency clinical trials. In some cases, these vendors have teamed up with networks of sites to provide clinical trial support. OSTP may wish to consider engaging with these vendors and network sites to provide both a source of "warm bases" for the clinical studies described in section 3.a.ii and the needed training and surge capacity. Already established partnerships between these types of vendors and clinical study sites would enable a faster start up time to clinical research activities to meet OSTP's goals.

c. Whether "warm base" research could be appropriately supported as: i. A demonstration project with commercial partnership., ii. A public-private partnership, iii. An agency-funded program.

A demonstration project involving several, already established networks of sites and partners throughout the U.S. may be a useful first step to gather evidence and support for the ability to set up a limited "warm base" research program. However, in order to truly have a "warm base" research program actively running clinical trials *and* ready and able to respond to immediate emergency clinical trial research, an agency-funded program would provide the best long-term support for the technical and other services required. A multi-year agency funded program with the ability to issue multiple contracts could also best leverage the national collection of existing activities and infrastructure to meet the overarching goals of designing a national clinical trial system. Using this already-existing infrastructure would allow OSTP to rapidly initiate their vision for a national "warm base" research program. Networks selected should demonstrate their ability to provide a large, diverse pool of potential participants and site agreements, the ability to recruit internationally, and provide past performance demonstrating training, activation, and support of clinical trials.

Topic 4: Emergency Master Agreement

a. Basic terms that might form part of an Emergency Master Agreement, including the following.

To rapidly stand-up clinic trials, OSTP should review examples of other established research networks and consortium agreements (such as the Cancer Research Network, the Children's Oncology Group). OSTP may wish to execute the Emergency Master Agreement with potential sites in advance to establish a set of default legal terms for studies. Special emphasis should be placed on using readily acceptable terms. Parties would be asked to accept terms to meet the minimum legal and regulatory requirements. The Emergency Master Agreement should contain a mechanism for adding individual studies via a work order with relevant additional terms that would override the default terms to meet special fact patterns. For example, studies in which the funding, investigational drug/device, or other elements are provided by a for-profit entity may require a departure from the default term regarding intellectual property, data ownership, publishing, or subject injury. This approach would minimize the time for study sites to review and negotiate the work orders.

i. *Data collection and use*

"Data" should include all data and information generated by the Institution in the performance of the study and required to be delivered in accordance with the IRB-approved protocol. Data should not include original Study subject or patient medical records, research notebooks, source documents, or other routine internal documents kept in the Institution's ordinary course of business operations, which should remain the property of the participating site. The sponsor's right to use the data should follow the signed informed consent and authorization form, applicable laws, and the terms of the agreement. The participating site should retain the right to use the data and results for purposes including publication, IRB, regulatory, legal, internal education, patient care, and noncommercial research, without the payment of royalties or other fees.

ii. *Publication/accessibility of trial data*

Participating institutions should be granted a right to use and publish data generated at their own site in performance of the study after the sponsor reviewed any manuscripts and requested removal of confidential information. The sponsor should not have any editorial control of the conclusions made in the manuscripts. This

right to publish should be delayed until primary study publication based on data from all participating sites is made, or the decision is made not to publish. It is not industry standard to grant each participating site access to study wide de-identified data. However, in publicly funded studies under the master agreement, the government may wish to provide each participating site this access upon conclusion of the study and/or publication of the primary study results.

iii. *Use of a single IRE* across all participating trial sites.

Standing up a dedicated emergency clinical trial IRB could be helpful long term, especially if that IRB extends its federal wide assurance (FWA) number to smaller trial sites that lack their own IRB. However, this would be a resource intense exercise. It may be more efficient to hire a central IRB such as WIRB to fulfill that function.

b. Additional terms for an Emergency Master Agreement

i. Confidentiality.

"Confidential Information" should include information disclosed and identified as confidential to the participating site by or on behalf of the sponsor to conduct the study and any data generated in performance of the study. There should be an exclusion of the data from the confidential definition for the purposes of publication. Otherwise, the confidential information terms would be fairly standard.

ii. Patents/intellectual property.

Any new inventions, developments, or discoveries made in the performance of the protocol, and which incorporate sponsor's confidential information ("Inventions") shall be promptly disclosed to sponsor. Title to Inventions which are enhancements, modifications, or improvements of the sponsor's study drug or study device and that are made during and in performance of this agreement shall reside with sponsor ("Sponsor Inventions"). The participating site should also be granted a license to use sponsor's inventions for its own internal educational, patient care, and noncommercial research purposes.

iii. Control of study drug.

Unless stated in writing by sponsor, all items are and will remain the sole property of the sponsor until administered or dispensed to study subjects during the study. Receipt, storage, and handling of study drug or study device will comply with all applicable laws and regulations, the protocol, and the sponsor's written instructions.

iv. Indemnification.

Oracle suggests basic broad indemnification rights for the study sites to maximize participation. This is particularly important in order to obtain participation from sites with limited or no research experience, which will maximize the diversity of Principal Investigators and participants. Any special considerations regarding indemnification could be added within study specific work orders to allow for private IP, funding, or other special considerations such as limitation of liability statute (i.e., the Public Readiness and Emergency Preparedness [PREP] Act). As such, OSTP may wish to consider the following language: Sponsor agrees to defend, indemnify, and hold harmless the institution … (collectively referred to as "Institution's Indemnitees"), from and against any third-party claims … (including reasonable attorney's fees) and suits alleged to be caused by or arising from the conduct of the study or use of the study drug or device under this agreement or from the sponsor's use of the study results ("claims"), regardless of the legal theory asserted.

v. Compensation for injury.

For studies without private sector funding or investigational drugs or devices, Oracle recommends that subject injury language similar to what is included in federal grant funding research (i.e., the Federal Demonstration Partnership template[10] language) be incorporated into the agreement. For studies involving private sector sponsorship, we suggest the language below. Oracle recommends inclusion of both versions in the Emergency Master Agreement, with language regarding when each version is applicable. Any special considerations regarding subject injury could be added within study specific work orders to allow for private IP, funding, or other special considerations such as limitation of liability statute (i.e., the PREP Act). If a study subject suffers

[10] https://thefdp.org/default/subaward-forms/

an injury directly caused by a {study drug/device} and/or any properly performed procedures required by the protocol, sponsor shall reimburse for the reasonable and necessary expenses of diagnosis and treatment of any study subject injury, including hospitalization, but only to the extent such injury is not directly caused by (i) institution's negligence or willful misconduct; (ii) the natural progression of an underlying or pre-existing condition or events, unless exacerbated by participating in the study; or (iii) institution's failure to adhere to and comply with the protocol and all written instructions furnished by sponsor for the use and administration of any {study drug/device} used in the study, provided that deviations from the protocol and written instructions for study subject safety concerns will not disqualify institution from reimbursement under this provision. These obligation terms are subject to modification in regard to a particular study as agreed to by the parties in a work order specific to a study executed after this agreement.

c. Input from key stakeholders on the content of Emergency Master Agreement terms.

Oracle recommends that established networks (including industry groups for sponsors, medical centers, and healthcare providers) be leveraged to collect feedback during the drafting process.

d. Facilitating stakeholders' understanding and adoption of the Emergency Master Agreement framework.

i. Any models for such adoption in related areas, such as the NCATS SMART IRB Platform.

Many large academic medical centers will be able to easily understand and adopt the Emergency Master Agreement framework, as it is similar to research consortia agreements. For healthcare organizations less familiar with this type of agreement, it may be beneficial for OSTP to partner with clinical research organizations or health IT organizations that have experience engaging these types of facilities in clinical trials.

Topic 6: International coordination and capacity

a. Designing domestic emergency clinical trials effort that coordinates with international ones.

Facilitating clinical trial participation, both inside and outside of the U.S., will require technology solutions and services that can accommodate large numbers of diverse studies in terms of size, complexity, and geography.

b. Identifying international sites that might be available to participate in emergency clinical trials.

Software platforms can automate and simplify clinical study start-up and allow teams to collaborate globally for site identification and selection using historical site data and feasibility management tools to identify high potential sites, maximizing efficiency.

c. Overcoming regulatory barriers that delay expansion of U.S. trials into international sites.

Software platforms and services can facilitate the identification of trial sites globally and provide visibility (through extensive analytics) into patient enrollment and progress. Such capabilities provide insight into historical and ongoing site performance thereby enabling effective decision making about recruitment and supplies management throughout the trial. These platforms and services should include features that align with global regulatory requirements (e.g., GCP) to ease acceptance across markets.

d. Tracking the clinical trial research initiatives under the G7 Trials Charter and Quad leaders' commitment to pandemic preparedness, and to harmonize with U.S. emergency clinical trials efforts.

A CTMS tool can improve operational efficiency by standardizing clinical operations workflows and providing real-time visibility to data across all study management processes. OSTP should look for a CTMS that can be configured to meet individual customer processes for all research studies and can be integrated with advanced analytics capabilities that provide timely, fact-based insights to drive informed decision making.

Appendix A: Definitions and Abbreviations Used in Oracle's Response

Term	What It Means
Achieve	Oracle and our clients benefit when we agree in writing to a set of standards for objective performance and intellectual property. When this phrase is used, it intends to mean that Oracle will comply with obligations that are codified in contracts with our clients.
Achieve	Oracle and our clients benefit when we agree in writing to a set of standards for objective performance and intellectual property. When this phrase is used, it intends to mean that Oracle will comply with obligations that are codified in contracts with our clients.
Best of breed	Any item or product considered to be the best of its kind.
CDC	Centers for Disease Control and Prevention
Commercial off the shelf or off the shelf	This phrase is not meant to imply that a product will meet a customer's business needs (or expectations) without any special configuration or customization. Instead, these are used to reflect the product's standard functionality. "Standard functionality" for an application is defined as the functionality described in applicable documentation for the application as provided by Oracle.
Configure or Configuration	The setup of the applications by entering specific values which drive business processes using the Standard Functionality provided within the Oracle application(s) without extension.
CRO	Contract Research Organizations
CTA	Clinical Trial Agreement
CTMS	Clinical trial management systems
DCT	Decentralized clinical trials
Develop or development	Oracle is, in part, a software development company. When we use the word "develop" or its derivatives outside of the context of how Oracle has built our standard suite of products, "develop" or its derivatives intend to mean that Oracle will comply with obligations that are codified in contracts with our clients.
EDC	Electronic data capture
EHR	Electronic health record
Enhance	When "enhance" is used in context of augmenting the performance of a product or system, Oracle means that the solution described in our proposal is believed to be able to assist you with addressing the business issues outlined in the RFX. Oracle does not use this word to imply a guarantee or warranty. Oracle will comply with obligations that are codified in contracts with our clients.
Ensure	Oracle and our clients benefit when we agree in writing to a set of objective performance and delivery standards. When this phrase is used, it intends to mean that Oracle will comply with obligations that are codified in contracts with our clients.

Term	What It Means
FDA	U.S. Food and Drug Administration
FQHC	Federally Qualified Health Centers
FWA	Federal wide assurance
GCP	Good Clinical Practice
Guarantee	Oracle undertakes commercially reasonable efforts on behalf of our clients. We cannot proffer guarantees or warranties at proposal stage. Any such terms are codified later, in contractual agreements with our clients.
HHS	U.S. Department of Health and Human Services
ICMJE	International Committee of Medical Journal Editors
Improve	When "improve" is used in context of augmenting the performance of a product or system, Oracle means that the solution described in our proposal is believed to be able to assist you with addressing the business issues outlined in the RFX. Oracle does not use this word to imply a guarantee or warranty. Oracle will comply with obligations that are codified in contracts with our clients.
Integration or integrate	Except to the extent expressly stated in the scope section of this document, the use of the terms "integrate" and "integration" throughout this document is not intended to mean that Oracle will address (i) the physical or functional integration of Oracle products with external legacy applications, third-party products, and/or other software applications; (ii) the functioning of Oracle products as a coordinated whole with such external legacy applications, third-party products, and/or other software applications; or (iii) any non-standard integration between Oracle products. Rather, the terms are used to refer to the overall concept of data exchange between the Oracle products and other applications, products, or applications identified in this document, and may include interfacing and/or other methods of integration or interoperation as described in the scope section of this document.
IRB	Institutional Review Board
LHN	Learning Health Network
Meet or exceed your needs, requirements, expectations, or similar	Oracle and our clients benefit when we agree in writing to a set of objective performance and delivery standards. When these phrases are used, they intend to mean that Oracle will comply with obligations that are codified in contracts with our clients.
NIH	National Institutes of Health
Oracle	Oracle Corporation
OSTP	Office of Science and Technology Policy
Out of the box	This phrase is not meant to imply that a product will meet a customer's business needs (or expectations) without any special configuration or customization. Instead, these are used to reflect the product's standard functionality. "Standard functionality" for an

Term	What It Means
	application is defined as the functionality described in applicable documentation for the application as provided by Oracle.
Partner or partnership	The term “partner” refers to and is interchangeable with “ally” or “collaborator”. Use of the term is not intended to, and does not, contractually or otherwise bind Oracle to the client, or create a partnership, joint venture or agency relationship between Oracle and the client.
PBRN	Practice-based research networks
PREP	Public Readiness and Emergency Preparedness Act
R0	Reproduction number/rate
RWD	Real-world data
Satisfy or satisfaction	Oracle and our clients benefit when we agree in writing to a set of objective performance and delivery standards. When these phrases are used, they intend to mean that Oracle will comply with obligations that are codified in contracts with our clients.
Solution	The term “solution” is not intended to, and does not, express or imply that Oracle can or will contractually or otherwise agree to “solve” any issues or problems.
Source code	Whether or not Oracle will provide source code for deliverables is evaluated on a project-by-project basis and may depend on the deliverables at issue. Oracle will comply with obligations that are codified in contracts with our clients.
Standard functionality	Base features and usability of the Oracle application without extension, enhancement, or modification
Success or successfully	Oracle and our clients benefit when we agree in writing to a set of objective performance and delivery standards. When these phrases are used, they intend to mean that Oracle will comply with obligations that are codified in contracts with our clients.
Support, supported, or not supported	“Support” and its derivatives have many meanings. “Supported” sometimes refers to whether a program is covered under a contract for technical support. In addition, "supported" may refer to whether a certain business process may be addressed using functionality contained in a standard product configuration. “Supported” may also be used to identify products or features that work together or are compatible. MyOracle Support provides technical assistance for Oracle customers. Oracle leadership lends their “support” to our teams on the ground. Because this RFX seeks information on a number of types of support, we drew heavily on context to create answers to the questions asked. Oracle will comply with obligations that are codified in contracts with our clients.
System	When Oracle uses the word “system,” we mean it to be a “platform” or “environment.” The use of the word "system" does not extend to Oracle any responsibilities to third-party components, systems, and/or products that you are responsible for when Oracle is only delivering our products or Cloud services. Oracle will comply with obligations that are codified in contracts with our clients.
WIRB	Western Institutional Review Board. The WIRB is a private IRB that frequently acts as a central IRB on both public and private clinical trials.

January 25th , 2023

RE: Office of Science and Technology Policy (OSTP): Notice of Request for Information (RFI) on clinical research infrastructure and emergency clinical trials.

Thank you for the opportunity to share ideas on enhancing clinical research infrastructure and emergency clinical trials.

The detailed RFI circulated by OSTP presents a thoughtful view of the challenges, some of which also surfaced in the January 12 Whitehouse Roundtable Discussion. Our aim is to provide perspective as a research organization with experience in infectious diseases and to spotlight relevant use cases and organizational models that can bring us closer to the goal of global pandemic preparedness.

Areas of focus	Comments and suggestions
Section 1.a (Centralized US-level governance structure)	We recommend a centralized Governance Board handling high-level decision making. Membership would include public agencies (NIH, FDA, CDC, DOD), commercial entities (pharma, CROs), and individuals representing the "patient voice" in diverse communities. This last element is a cornerstone for building trust and combatting misinformation. Roles of committees, bylaws, and procedures would be defined in a governance charter, and the Board would have authority to implement changes in oversight and propose alterations to recruitment plans, project management, and other strategic functions. Timing of these responses would depend on the rapidity of pandemic spread.
Section 1.b Criteria determining need for research	Minimum criteria: WHO designation of a pandemic; Outbreak of disease within population groups across multiple states; Declaration of public health emergency; Presence of a novel pathogen with no safe and effective therapy; Significant mortality and high hospitalization rates.
Section 1.c Factors determining what types of studies are needed	Key factors: Pandemic or epidemic designation by relevant public health agencies; Meeting an agreed-upon threshold in the ratio of hospitalized versus non-hospitalized patients; Need for mechanical ventilation or other invasive procedures; Mortality rate greater than that of seasonal influenza; Transmissibility, meaning ease of infection after exposure and mode of transmission—i.e., respiratory versus skin contact.

Areas of focus	Comments and suggestions
Section 1.d How to communicate decisions to institutions and trial networks	Recommendation: create a central registry of participating institutions/sites to be alerted electronically. Points of contact at each institution would be identified in advance to receive automated secure text/email messages. A central Institutional Review Board (IRB), established and maintained for emergency clinical trial response, would be notified simultaneously so the review process can commence. Protocol (s) would be sent via secure electronic message to institutions, networks and oversight bodies such as IRBs. A separate national database of potential subjects akin to organ transplant registries would be maintained to help recruitment, especially in the beginning stages of any emergency trial.
Section 1.f Procedures for overseeing development of trial protocols and selection of study agents	The Governance Board described above (1.a) creates oversight procedures. Committees under the Board's purview would mediate among competing proposals for vaccines, drug treatments, surgical interventions, etc., and prioritize programs within the clinical trial network. FDA advisory committees could serve as a model for ensuring Board representation by a mix of healthcare stakeholders including clinicians, academic experts, and members with experience in healthcare communications. Groups under the Governance Board also would craft and activate public service campaigns supporting trial participation and maintaining ready-to-launch, message-tested influencer campaigns that speak to needs and motivators across diverse communities. The goal is to foster trust in the process and increase chances for rapid acceptance of the drugs or vaccines when ready.
Section 1.g Designing trials to capture data without unnecessary complexity	COVID-19 vaccine trials in the UK and Israel made good use of so-called master protocol approaches in which subjects are enrolled into multiple arms of a study sharing a single placebo control arm. This approach relieves pressure on enrollment, reduces the number of patients "wasted" in control arms, and (in theory) might help impose discipline to limit the number of poorly designed or underpowered studies. Both the US and the UK effectively employed master protocol methods in testing therapeutics in the ACTIV public-private partnership and the RECOVERY trial, respectively. These demonstrated utility both in hospitals and outpatient settings. The challenge is initiating such trials early in—or ahead of—a global emergency. One option in the US is to maintain ACTIV or other master protocol studies as part of a "warm base" initiative, using the trials to test yearly or novel vaccines against respiratory viruses such as flu and RSV. Barriers to rapid implementation of such protocols should be systematically studied and removed as soon as they are identified.

Areas of focus	Comments and suggestions
Section 1.h Best practices for enrolling vulnerable populations	Recommendation: employ existing best practices with respect to informed consent forms (ICFs and e-ICFs). Where possible, use decentralized and mobile trial approaches to bring the study to the subject. Expedite use of public transportation buses, school buses and other vehicles for this purpose, staffed in some cases by community volunteers, fire and police departments. To foster readiness in "quiet times," these units will also run once- or twice-yearly trainings/drills/simulations, perhaps using AI-enhanced gamification tools to bolster engagement in simulations. Simultaneously, clear the way for municipalities to quickly convert shuttered schools into trial and/or vaccination sites.
Section 1.j Appropriate entities to manage trials	Recommendation: engage CROs for project oversight, monitoring clinical trial progress and data management. CROs have systems in place to carry out these functions. Other possible entities include government-contracted data management firms already integrated into federal systems.
Section 1.l Criteria to govern researchers' access to trial data	Siloed data collection is a barrier to data sharing in an emergency. But encouraging models for mediating competing interests exist. One is UK Biobank, which lets collaborators access large datasets in real time, analyze rapidly emerging trends and make recommendations to governance bodies. In the US, a global data-sharing and analytics platform called Vivli has 7,000 clinical trials in its inventory, contributed by 45 members. In emergency trials, and especially in decentralized studies, principal investigators and other researchers should be equipped to oversee enrollment of subjects across state lines, with access to data via open data portals as NIH has done for repurposed drugs. Such portals can be incorporated into "mega sites" operating virtually to facilitate recruitment across geographic boundaries. In an emergency, a national licensure pathway for emergency trial participation would skirt requirements for state licensure. The same framework would enable nurse practitioners and others to act as sub-investigators, with access to the same central data repository.
1.l.2 Identifying and incentivizing Research institutions and networks; Building	While private companies will require few inducements to join large-scale research initiatives with government and/or philanthropic backing, incentivization is more complicated in the case of study subjects and site staff. As Lisa Fitzpatrick noted in the Jan 12 Whitehouse Roundtable, people from diverse communities who participate in "warm base" trials, whether as investigators or study subjects, must have a window onto benefits of participation beyond simple altruism. One challenge is

Areas of focus	Comments and suggestions
diversity and equity	educating the public on the benefits of joining such an endeavor—which, for trial subjects, may include access to the best care in the event of an emergency. Government programs should partner with nonprofits such as Greater Gift that are devoted to boosting clinical trial awareness in underserved communities. As for engaging site staff, part of the message we must communicate is that clinical research can be a career opportunity. To make this point effectively, however, the medical profession must start to address poor compensation levels for careers in infectious diseases, which impair our ability to nurture talent. In the US, Congress can begin by funding a pilot loan repayment program for people who work in infectious diseases and health emergency response, as proposed under the Inflation Reduction Act (news coverage here.)
Section 2.b Increase participant diversity and research presence in underserved areas.	In the US, FDA and Congress have strengthened requirements around clinical trial diversity, both as draft guidance and in diversity-related provisions in the Consolidated Appropriations Act, 2023. If a disease or condition disproportionately affects a particular patient population, enrollment numbers must reflect the difference in impact. In theory, over time, this will increase the number of trial sites in underserved areas and increase diversity of study participants and investigators—both in "quiet times" and during pandemics. Absent data showing disproportionate impact in some populations, the baseline enrollment targets for racial and ethnic-minority participants should mirror their representation in the US population. Noncompliance with these requirements may justify withholding regulatory approval for products under study. Outreach and collaboration with trusted organizations in underserved communities can help reach the goals. But these collaborations should be evaluated by government (AHCPR), philanthropic, and academic entities to assure meaningful partnership and to inform future efforts. Our system should also encourage recruitment of Federally Qualified Health Centers (FQHCs) in efforts to increase clinical research capacity within underserved communities.
Section 3.a.i "Warm Base" research and disease areas relevant to underserved communities	NIAID has developed a "warm base" model of collaboration where sustained research support, independent of a specific study or grant, forms a foundation that can be rapidly leveraged to strengthen clinical research capacity and readiness. This model of research support could also help increase the number of clinical investigators with diverse backgrounds and sites in underserved and/or concentrated minority communities while augmenting efforts to recruit a more diverse patient population. Logically, the "warm base" approach in these communities would focus on infectious

Areas of focus	Comments and suggestions
	diseases that disproportionately affect the community, with at least two objectives: First, to enhance "quiet time" (non-pandemic) clinical care for these populations; Second, to provide surge capacity at both staff- and subject-level in pandemic emergencies. In some cases, as a starting point, warm base initiatives in underserved communities could leverage ongoing clinical research initiatives by Walgreens and other retail pharmacies.
Section 3.c Funding models for "warm base" research	While demonstration projects with commercial partners could increase surge capacity, achieving an impactful "warm base" research network requires long term, stable funding commitments by federal and state governments and philanthropic organizations. There are models if we look beyond a rigid definition of warm base. Under NIH, the National Cancer Institute runs a National Clinical Trials Network (NCTN) that achieves much of what we envision for warm-base pandemic research networks. In addition to helping set standards of care and testing new treatments, the organizational structure allows for large-scale patient screening with molecular precision. Under a federal advisory committee, NCTN maintains diverse funding channels, outreach and support for community hospitals and a harmonized network of tissue banks with digital records of stored samples, clinical details including treatment response and sophisticated tissue re-use consent protocols.
6. International coordination	Recommendation: create a special protocol assessment pathway to fast-track emergency trial protocols that satisfy both domestic and international regulatory agencies. This may require additions to the Code of Federal Regulations and corresponding international rules. In parallel, we should create a pandemic or emergency regulatory agency with membership from different regulatory bodies—modeled on the UN Security Council with permanent and rotating memberships and charged with international oversight, review, and approval, but without disconsonant veto powers. Manufacturers and CROs would collaborate extensively across borders in North America, Europe, Asia-Pacific, Africa, Latin America and other regions. Many of these industry-developed networks already have infrastructure to quick-start vaccine studies in multiple regions simultaneously. What's lacking is superstructure to coordinate emergency activities across networks that are exclusively contracted with for-profit enterprises. The bigger agenda point, not referenced in the RFI, is how to ensure that diversity-related measures tailored to US initiatives resonate in international contexts. As in the US, emergency international frameworks should embrace enrollment requirements such that populations experiencing the greatest disease

Areas of focus	Comments and suggestions
	impact are proportionately represented in studies. While data-gathering and analysis in diverse populations is critical to success for a global project there are pitfalls. For example, in global trials, the enrollment of subjects in Africa or Latin America should not, by default, be credited toward the numbers of African Americans and Hispanics that must be enrolled to show that US-based trials are equitable.

About this submission

Syneos Health® (Nasdaq:SYNH) is a biopharmaceutical solutions organization that integrates clinical development, medical affairs, and commercial capabilities. We have many years of experience running global clinical trials and commercial campaigns in infectious diseases and other therapeutic areas for a broad spectrum of biopharmaceutical companies. The goal of this submission is to share insights that can help advance global pandemic preparedness. It's difficult to imagine a more urgent public health priority.

Sincerely,

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January 25, 2023

Office of Science and Technology Policy

RE: RFI on Clinical Research Infrastructure and Emergency Clinical Trials

Comments submitted electronically via
datacollectionforclinicaltrials@ostp.eop.gov

The American Medical Informatics Association (AMIA) appreciates the opportunity to provide input to the Office of Science and Technology Policy (OSTP*) Request for Information (RFI) on Clinical Research Infrastructure and Emergency Clinical Trials.* AMIA is the professional home for more than 5,500 informatics professionals, representing frontline clinicians, researchers, and public health experts who bring meaning to data, manage information, and generate new knowledge across the health and healthcare enterprise.

AMIA commends OSTP for its focus on efforts to protect the public health in cases of national emergency. An established research infrastructure, uniform protocol for the conduct of emergency clinical trials, and responsible data sharing and oversight requirements should be viewed as necessary components of a national preparedness plan. Only with integrated, longitudinal data at the patient level, can we monitor acute events, formulate appropriate interventions for harm prevention and reduction, fairly allocate resources to mitigate effects in a timely way, and track, predict and measure the effectiveness of interventions. The integrity and security of our health data infrastructure and nation should be a priority to support situational awareness and enable coordinated leadership action.

Clinical Trial Governance and Standards

AMIA supports a federally coordinated and harmonized national regulatory and/or policy framework for the conduct of emergency clinical trials, as well as data acquisition, management and sharing policies with rapid, reliable reporting of results to one centralized authority, with results easily distributed to engaged participants. These requirements should include, emphasize and leverage digital health data resources for standardization of data elements, interoperable data sharing, population health and reporting of results.

Given the emergency nature of these clinical trials, pre-determined yet flexible standards for data elements, clinical trial study design, requirements to research large populations of patients, and technological infrastructure needed to support these processes, requires strong multi-agency and multi-stakeholder coordination.

Emergencies often result in changing the rules for how we do things and may compromise individual rights to protect public health. To prevent long-term compromise to individual rights, such as autonomy and privacy, it is important that justification for an emergency clinical trial is clearly defined, along with what would constitute an end.

When clinical trials are accelerated, oversight might be less stringent. In these cases, transparency is paramount. This includes transparency about deviations from normal clinical trial protocols (in terms easily understandable by the public), and transparency about data as they emerge so the public can participate in the oversight process.

Regarding standards, stakeholders and experts from the FHIR Accelerator community, in particular, Gravity and Vulcan, should be included in planning to support advancing technological standards for the infrastructure needed to execute an emergency clinical trial system that is proactive as well as reactive. Standards for data captured should align with USCDI V.4, as the data elements in V.4 are increasingly comprehensive and can potentially support a baseline federated model for data capture in emergency clinical trials. Given the population-level data needs, data sharing/exchange, and data reporting, it is recommended that stakeholders from the SMART/BULK FHIR be consulted and included to provide standards tracking patients enrolled in study sites.

Data Sharing

The advantages of data sharing can only be realized with appropriate levels of investment in underlying infrastructure, including tools for managing, storing, and indexing increasingly large and diverse data sets, as well as human resources for curating shared data. AMIA encourages OSTP to leverage resources across federal agencies and programs to develop necessary infrastructure for emergency clinical trials. We also encourage the incorporation of the FAIR data principles (findable, accessible, interoperable and reusable) to optimize the use of resources and data.

The conduct of clinical trials in emergency settings without technological enablement/assistance would slow innovation in our data and tech-rich healthcare ecosystem of the 21st Century. Digital data technology is an asset in this context, one that will need stakeholder engagement to steward, coordinate and organize. Marquis-Gravel (Technology-Enabled Clinical Trials | Circulation (ahajournals.org) addresses transforming evidence generation. JAMIA has published several studies focused on technology and clinical research that may provide guidance for the development of emergency clinical trial requirements. For example: NelsonSJ et al (EHR-based cohort assessment for multicenter RCTs: a fast and flexible model for identifying potential study sites | Journal of the American Medical Informatics Association | Oxford Academic (oup.com) addresses study site identification. WynerZ et al (FDA MyStudies app: a reusable platform for distributed clinical trials and real-world evidence studies | JAMIA Open | Oxford Academic (oup.com) addresses privacy, engagement, and extensibility in mobile clinical research. Zayas-CabaanT et al (National health information technology priorities for research: A policy and development agenda | Journal of the American Medical Informatics Association | Oxford Academic (oup.com) focuses on policy considerations.

Additionally, an integral component of data management, especially in cases of emergency, is an investment in public health informatics workforce training to build competencies and capacity at every level where information is generated, managed, and used for population health. We also encourage the establishment and sustainability of Centers of Excellence for public health informatics to serve as models of best practice for the nation. These Centers could be mobilized for

technical resource and practice runs, including focused inclusion of under resourced and underserved communities.

Identifying and Incentivizing Research Institutions and Networks; Building Diversity and Equity

Planning and engagement with traditionally excluded communities for clinical trial research in emergency situations will require advanced engagement and intentional co-design with these communities. FloresL et al (Assessment of the Inclusion of Racial/Ethnic Minority, Female, and Older Individuals in Vaccine Clinical Trials - PubMed (nih.gov) provide insights into how to engage these communities. Cunningham-Erves (Engagement of community stakeholders to develop a framework to guide research dissemination to communities - Cunningham-Erves - 2020 - Health Expectations - Wiley Online Library) provides some practical insights and experience for engagement of traditionally-excluded communities in clinical trials. It is recommended that researchers and scholars, including many of our AMIA members from these communities be engaged in policy and planning efforts for emergency clinical trials.

Data Privacy and Protection

Consideration of data privacy and protections may be understated in this RFI. In all cases, data sharing should preserve and protect an individual's privacy and autonomy. An individual's privacy protections must be consistently maintained, and their privacy preferences respected across clinical, research, community services, and commercial use of their health data.

Informed consent requires clearly worded, understandable explanations of how an individual's health data will be used and the circumstances in which it will be disclosed. Health data must always be collected, managed, and shared in ways that minimize the risk of reidentification of individuals. For emergency clinical trials, solutions are needed to support and manage enduring and/or emergent consent, where participants can update their consent preferences real time.

The threat of communicable risk, contaminant risk, and other threats to public health necessitates broad access to health data, but there must be severe penalties for misuse.

Thank you or your consideration of these comments. If you have any questions, please contact Tayler Williams, AMIA Public Policy Manager, at twilliams@amia.org.

Sincerely,

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Response to RFI: Clinical Research Infrastructure and Emergency Clinical Trials
Document Citation: 87 FR 64821

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We [National Institute of Allergy and Infectious Diseases (NIAID) sponsored Infectious Diseases Clinical Research Consortium (IDCRC)] representing the nation's ten Vaccine Trials Evaluation Units, (VTEUs) https://idcrc.org/] are writing in response to this RFI based on our engagement and leadership (2020-present) in the pivotal COVID-19 prevention (e.g. vaccine, mAb) and therapeutic (small molecule/drug) clinical trials. The extramural IDCRC and VTEUs work in tandem with NIAID and other federal agencies as a coordinated national and global network of scientific experts to develop and test vaccines and other therapies to combat infectious diseases. In early 2020, we were mobilized to plan and successfully conduct at IDCRC sites the first phase 1 mRNA (Moderna) vaccine trial (began 65 days after sequence of the virus available). The data on this trial were collected and published on July 14th, 2020. Subsequently, the IDCRC, as part of the COVID-19 Prevention Network (CoVPN), was instrumental in the design, conduct and leadership of the five large (136,000 participants) Phase 3 trials of COVID-19 vaccines leading to multiple FDA vaccine authorizations and approvals, one of the first (the Moderna mRNA vaccine) was authorized in Dec. 2020. VTEU investigators were co-principal investigators on each of these trials. Other ongoing IDCRC COVID-19 trials (2020-present) include the mRNA vaccine boost and variant studies, "Mix and Match" of different COVID-19 vaccines, pediatric (Kid-Cove) and pregnancy studies (MOMI-Vax) of COVID-19 vaccines, and leadership in the COVID-19 vaccine Variant Immunologic Landscape Trial (COVAIL). We also were a leading network in the Adaptive COVID-19 Treatment Trials (ACTT1-4) the latter showing the value of

remdesivir, baricitinib and corticosteroids. These trials have significantly influenced US and international public health policy, and secondary analysis of data, including correlates analyses, continue to inform updated policy recommendations and approvals of secondary generation vaccines.

IDCRC does not agree with elements of the first basic premise in the RFI:

"The lack of a coordinated approach to clinical trials research in emergency settings has slowed the development of actionable information, which has in turn delayed the availability of vaccines, therapeutics, and diagnostics; and may also impede the tracking of the outbreaks themselves. Without some mechanism to coordinate and organize research on a larger scale in an emergency setting, researchers and decision makers are left with a series of relatively small, often inconclusive studies, and assembling data for larger-scale analysis is challenging."

There was a rapid mobilization of our network first by NIAID and subsequently by NIH and the public-private partnership Operation Warp Speed (OWS) now the USG Countermeasures Acceleration Group and the White House COVID-19 Response Team. The studies of the IDCRC, ACTT Consortium and CoVPN conducted in this public health emergency both in the US and at global sites were not only rapid but of very high quality and incredibly impactful (https://pubmed.ncbi.nlm.nih.gov/36689221/) . The studies demonstrated safety and efficacy of new vaccines and vaccine technologies, established successful therapeutics, and have saved millions of lives. As an example, these studies contributed to our global vaccine leadership that the US continues to enjoy, have led to effective treatment options for COVID-19, resulted in the effective vaccination of US and global populations, and identified vaccine and therapeutic products that should not be pursued. A similar success story can be said of the NIH RADx initiative in advancing new COVID-19 diagnostic technologies.

Decisions that impact public health must be built on rigorous scientific data. Product selection for trials must have a solid scientific basis and demonstrate safety in preclinical studies. Products with faulty design or poorly designed or executed clinical trials will not give clear answers and may in the end be harmful. While health care providers must be engaged in understating the value of clinical trials, most are not trained in the science or rigor of clinical research, and crucial regulatory (e.g., human subjects protection and informed consent, documentation) requirements for such research. We cannot rely on anecdotes, cases series, observational studies, or "pragmatic" studies to substitute for rigorous clinical trials. Hydroxychloroquine is a key example of this point. Bottom line we need to have a national infrastructure supporting training of clinical trialists and an infrastructure ready to respond to national emergencies.

The current U.S.-level governance structure: HHS ASPR coordinating with NIH, BARDA, DOD, FDA can be improved and streamlined but is an appropriate governance structure for coordinating the US approach to clinical trials research in emergency

settings. We do strongly support the efforts to improve and modernize electronic data entry and clinical trial data collection across trial sites that can be scaled up for use in emergency research settings but under an umbrella of a rigorous clinical trials infrastructure.

IDCRC strongly agrees with a second premise in the RFI

"a key issue is to support the expansion of clinical research into underserved communities and increase diversity among both trial participants and clinical trial investigators"

Both increased diversity in trial participants and diversity in clinical trials investigators need better planning and additional governmental leadership and resources. An example of an effective approach to educate underserved communities in clinical research was developed by the CoVPN for the phase 3 COVID-19 vaccine trials and included the CoVPN Community and Stakeholder Engagement Strategic Plan (attached) and launched the related CoVPN Faith Initiative https://www.coronaviruspreventionnetwork.org/about-covpn/. The enrollment at CoVPN sites of underrepresented minorities in the Phase 3 vaccine clinical trials was exceptional. (https://pubmed.ncbi.nlm.nih.gov/36689221/)

The second component "enhancing diversity among investigators" is also strongly endorsed. We recognize the need for formal training in the discipline of clinical research and vaccinology has never been greater. We are positioned to equip a new generation of scientists with the necessary tools to enable them to explore, create, innovate and implement the vaccine and treatment programs of the future. As successful examples we highlight the IDCRC Mentorship Program https://idcrc.org/training/index.html and the Early Career Investigator Pilot Awards https://idcrc.org/training/pilot-grants-program.html providing mentorship, professional development and funding of early career investigators and fellows in clinical and translational infectious diseases research. Also, the CTSA infrastructure supporting education (Master's level degrees) and training in clinical and translational research is another example. Our program continues to innovate and incorporate new technologies, strategies, data analytic tools and educational approaches to prepare the next generation of leaders in clinical and translational research.

In summary, we wholly endorse the need for clinical trial infrastructure, and put forth the IDCRC and VTEUs as an example of how investments in time, talent, leadership and infrastructure were key to the rapid and successful COVID-19 response in the U.S. We endorse using this already strong program as a foundation from which to build a more robust and diverse emergency response infrastructure in the US.

RESPONSE TO OFFICE OF SCIENCE AND TECHNOLOGY POLICY (OSTP) REQUEST FOR INFORMATION POSTED 10/26/2022

Respondent: This response is on behalf of a global clinical trials network called INSIGHT (International Network for Strategic Initiatives in Global HIV Trials).

Introduction

As background, INSIGHT was initially funded in 2006 by the National Institutes of Health, National Institute of Allergy and Infectious Diseases (NIH/NIAID) to design and conduct global HIV randomized trials. [1-3] In 2009, our mission was expanded to conduct research on influenza. [4]

In 2020, INSIGHT was selected by the NIH-led public private partnership Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) group to lead a collaborative global network of networks to develop a master protocol, known as ACTIV 3, to study investigational antiviral agents for hospitalized adults with COVID-19 in randomized trials and, in doing so, expanded the number of sites and scientific expertise in the treatment of acute respiratory disease and critical care medicine. Additional collaborative networks included the Prevention & Early Treatment of Acute Lung Injury (PETAL) and the Cardiothoracic Surgical Trials Network (CTSN), both funded by the National Heart Lung and Blood Institute (NHLBI), and the US Department of Veterans Affairs. Like INSIGHT, each of these groups had initiated COVID-19 research prior to joining forces. [5-9] This collaboration led to the TICO and ITAC trials. [10-14]

In 2022, as part of a larger pandemic preparedness effort, ACTIV asked the ACTIV clinical trial groups conducting studies in hospitalized patients, ACTIV 3, ACTIV 5, and ACTIV 1 to join to form one clinical trial group to advance pandemic preparedness and response to respiratory pathogens, and to prepare a master protocol known as Strategies and Treatments for Respiratory & Viral Emergencies (STRIVE) (NCT05605093). The intent of combining the three ACTIV protocol groups was to develop a global clinical trials network inclusive of expertise in infectious diseases, critical care, pulmonary medicine, and emergency medicine. The STRIVE group continues to receive support via ACTIV including NIAID and NCATS. The STRIVE master protocol can be used to study treatments for any respiratory pathogen during a public health emergency, not only for participants hospitalized with COVID-19. INSIGHT continues to serve as the STRIVE statistical and data management center. To implement STRIVE, INSIGHT was further expanded to include sites of the French ANRS Emerging Infectious Diseases in France, a funding and coordinating Agency that has conducted several trials on COVID-19 and other emerging infectious diseases. [15,16]

The STRIVE collaborative group includes 130 U.S. clinical sites and 102 sites in 34 other countries across 6 continents that collaborate with 9 International Coordinating Centers (ICCs), a central Statistical and Data Management Center (SDMC), a central biorepository, and a pharmaceutical services company that provides investigational agents to sites to design and carry out randomized trials. We have a strong track record of more than two decades of collaboration with pharmaceutical industry.

Our responses to topics within this RFI are based on lessons learned during the conduct of COVID-19 trials and collective experiences conducting global randomized trials for more than 25 years.

Our responses are organized according to the 6 topic areas that were highlighted in the RFI.

1. Governance for emergency clinical trials response

We support a governance model similar to that described in the RFI. There should be an executive committee led by NIH and with inclusion of other Federal agencies, in particular the Food and Drug

Administration (FDA) and the Biomedical Advanced Research and Development Authority (BARDA). It should also include representatives from international regulatory groups and funding agencies, industry, and members of the global clinical trials network(s) chosen to develop the protocols and carry out the research.

We propose an executive committee with broad international membership because there are many regulatory challenges that impede rapid implementation of international research. These challenges include a lack of harmony internationally in: 1) protocol review by regulators, institutional review boards, and ethics committees; 2) the labelling of study treatments; 3) the shipment and importation of study treatments; 4) contractual agreements with clinical trial sites; 5) guidelines for sharing data; and 6) the collection and transportation of specimens for future research.

The executive committee should oversee the development of master protocol(s) to be used in emergency situations in the future. This group would also determine when large scale clinical research is needed and recommend "warm base" research that would be ongoing to ensure rapid implementation of trials for a public health emergency.

It is important to be able to rapidly conduct trials on preventive treatments, including vaccines and therapeutics for pre- and post-exposure prophylaxis, and trials on treatments for individuals who acquire the disease. The latter will include trials for outpatients with less severe or early disease and for hospitalized patients with severe disease. Our recommendations on the governance model are likely applicable to develop a structure for these different types of clinical trials. However, as noted in the introduction, INSIGHT's recent experience and the recently developed STRIVE protocol is for persons hospitalized with COVID-19.

The clinical trials network should include sites in low- middle- and high-income countries (LMIC/HIC) in all regions of the world. The network should have an experienced statistical and data management center, an infrastructure (e.g., international coordinating centers) for coordinating the work of several hundred sites around the world, a central biospecimen repository, and a group that can work with government agencies and pharmaceutical companies to rapidly distribute study treatments to sites.

An independent data and safety monitoring committee that will regularly review interim results (unblinded data) for trials conducted should be included in the planned structure.

Most clinical trials to establish the efficacy of potential treatments for emerging diseases can only be carried out during outbreaks of the disease. Thus, prioritization of trials and timeliness in conducting those trials is paramount. To that end, two advisory committees should be established: one that prioritizes pathogens and vaccines and therapeutics to study in trials, and one that advises on accelerating and coordinating regulatory reviews of clinical trial applications in the U.S. and in other countries to ensure rapid trial implementation.

Criteria for deciding whether to implement coordinated large-scale clinical trials that the proposed Executive Committee should consider include the scope and pace of the outbreak, the availability of potential preventive treatment and therapeutics, expected morbidity and mortality, transmissibility of the pathogen, and the feasibility of rapidly implementing the trial. If there are potentially effective treatments, they should be studied in randomized trials even if only phase 1 data exist. In this regard, treatments with limited data were studied in phase 2/3 trials during the 2013-2016 Ebola outbreak[17] and during COVID-19. [10-14]

Although early studies of novel pathogens that are carried out by the network may include epidemiological investigations to quantify characteristics of disease and to determine risk factors for infection and disease outcomes, randomized trials of potential treatments and the rapid completion

of such trials should be the primary goal. It is important to be able to initiate randomized trials rapidly once a need for emergency clinical research is determined.

Established clinical trials networks willing to collaborate with one another, and that have a large international reach, should be identified before emergency clinical trials are needed. Such networks should be able to carry out relevant "warm-base" research (see section 3 below). Once a decision is made to begin emergency clinical research, the executive committee and the chosen network(s) should be able to identify the sites to carry out the trial. If an infrastructure for the clinical trials network is established for "warm-base" research before emergency research is required, the network(s) responsible for the research should be able to respond to questions concerning timelines for regulatory and ethics approvals, enrollment estimates, the location of sites, and the number of study participants to be included in the research. The network should include sites with wide global coverage that serve diverse populations (e.g., race/ethnicity, geographic diversity). Substantive experience working with sites develops over time. Knowledge about site capabilities with regards to start up, enrollment and follow-up is essential to identify sites that should be prioritized for participation in emergency research.

The speed of regulatory approvals and the amount of study drug that is available to send to sites are important considerations in determining how many and which sites can participate in emergency research. The proposed executive committee and advisory committee on drug selection should ensure that an ample supply of investigational agents with sufficiently long shelf lives from pharmaceutical companies are available to be shipped to an experienced group that can provide it to sites.

Simplicity of design and trial implementation procedures are critical for both rapid implementation and reliable trial results. Inclusion/exclusion criteria for trials should be broad, data collected prior to randomization should be focused on key demographic and prognostic factors, and clinical efficacy and safety outcomes should be defined to focus on events that matter. It will be important that regulatory agencies help refine this approach and endorse it.

Children and pregnant women are often excluded from clinical trials and safety information is therefore more limited for those groups for treatments that are found to be effective. Some vulnerable populations are excluded because of the nature and location of sites. This can be avoided if inclusion/exclusion criteria are broad, and trial networks include diverse sites around the world.

Trials can be designed to initially enroll a target population for which safety is not a concern, but after establishing early safety (for example, in adults) be expanded to include children. Such designs have been implemented for vaccine trials to prevent Ebola virus disease[18].

In section 2 below, we have noted that experienced networks exist that can work together to conduct clinical trials during an emergency. It is important that the network(s) include international coordinating centers in different regions of the world to work with sites, handle enrollment projections and track enrolment; an experienced statistical and data management center to monitor the progress of clinical trials, timely entry of information into a central database that can be rapidly summarized for interim analyses; and collaborators that can serve as a central biorepository and drug distribution center.

We recommend that a central database be established with clinical trial data collected according to a common protocol. As noted in section 5 below, the data collected should be focused. Similarly, we recommend a central specimen biorepository be established that provides uniform specimen collection supplies to sites and works closely with the central statistical and data management center to track specimen shipments to the biorepository and to identify specimens for approved research

described in the protocol informed consent. The data and specimens collected should be accessible to researchers once the trial has been completed and the primary results have been published. Results should be published rapidly, which requires experienced investigators and statistical support.

2. Identifying and Incentivizing Research Institutions and Networks; Building Diversity and Equity

We have three recommendations for identifying institutions and sites to participate in clinical trials during an emergency:

i. Identify sites that are already participating in funded networks. These networks may be funded by the U.S. government or by governments in other countries. This was the approach taken in building the STRIVE network mentioned in the introduction, which includes over 200 sites, approximately 50% in the U.S. and the remainder in over 30 other countries covering all continents except of Antarctica.
ii. Incentivize networks to develop clinical trial sites in non-academic community hospitals that serve traditionally underrepresented populations with support for training clinical research staff.
iii. Build an infrastructure for conducting clinical trials that includes several international coordinating centers working in different regions of the world with knowledge of handling sponsorship functions. These international coordinating centers can leverage their current work to expand to other sites in their region, incl in LMIC.

These three approaches for identifying sites will increase the diversity of study participants and investigators. Participant diversity can be increased further by protocols that minimize participant travel and time commitments, and by the engagement of sites and investigator teams with a strong history of enrolling participants from historically underrepresented groups.

There are several ways to incentivize sites and networks to participate in clinical trials during a public health emergency. Firstly, ongoing research activities for personnel to perform between pandemics – see section 3 below – are critical. Secondly, the protocol should address key medical questions that investigators and their colleagues want answered, have broad inclusion and exclusion criteria that facilitate rapid accrual, minimize the number of in-person visits after hospital discharge, and take an approach to adverse event monitoring and reporting that focuses on capturing key clinical events and avoids overly burdensome data collection. Thirdly, trial budgets should be provided that cover the cost of conducting trials and providing sites level expertise and commitment. Finally, there should be opportunities for investigators to lead clinical trials and write manuscripts, and opportunities to promote the career advancement and training of junior investigators.

It is important for trial networks to consistently strive for increased diversity among investigators. This requires a strong commitment to intentional action for ensuring diversity, equity, and inclusion.

Community outreach and input can be obtained from a community advisory board with geographic representation. Such boards have provided important contributions to HIV, ARDS, and other research areas for decades. The INSIGHT community advisory board has advised on consent forms and educational materials, which are prepared in many languages for study participants.

The planned data collection pilot program is important and can be implemented as part of the “warm base” research. The pilot program should address the extent of data collection as well as novel technologies for capturing the data.

3. "Warm Base" Research

We agree with the authors of the RFI that in advance of an outbreak or other emergency there is value in having networks and sites begin carrying out clinical trials to create a "warm base" of clinical research capacity.

By capitalizing on existing, proven, clinical research networks, sites in those networks can leapfrog the lengthy "build" stage (e.g., hiring and training staff), and jump directly to the launch of protocols during public health emergencies.

Establishing a "warm base" model is essential to ensure the core complement of clinical research resources required to rapidly implement clinical trial(s). The "warm base" model will:

- Develop the broad scope of knowledge, skills, and abilities of the clinical staff, including but not necessarily limited to areas such as informed consent, good clinical practice, regulatory requirements, and data collection procedures.
- If an outbreak or other emergency occurs, enable initiation of protocol development and regulatory approvals for new trials under the infrastructure and funding provided by the "warm base" while additional funding is secured as required.
- Enable initiation of expanded contracts with clinical sites and other key groups such as a statistical and data management center, a specimen repository, and drug distribution if additional resources are required to supplement the "warm base" in an emergency.

Given the underlying nature of most public health emergencies, it is important that networks conducting "warm-base" research have investigators/clinical researchers with expertise in infectious diseases and in the treatment of critically ill populations. This is particularly important for research on treatments for hospitalized patients.

An example of "warm-base" research could be the study of treatments for severe influenza or other respiratory infections, and short term and long-term organ damage caused by these infections. Such research would benefit from sites in both hemispheres.

As noted in the RFI, the "warm-base" research can be used to provide training to less experienced sites and to build capacity in the event of a surge. We recommend a decentralized model in which site training materials are centrally developed and then locally tailored for sites in different regions of the world. Patient education materials should be developed similarly.

4. Emergency Master Agreement (EMA) for Clinical Trials

According to the RFI, the goal of developing an Emergency Master Agreement is to shorten the time it takes to begin emergency clinical trial research. The RFI mentions several terms which might be included in an Emergency Master Agreement with clinical trial sites or a network of sites. In general, we recommend that the executive committee described under Section 1 above develops standard language for such an agreement. The agreement should be concise and reflect their use for international sites as well as sites in the U.S. This recommendation reflects our belief that shortening the time it takes to begin emergency clinical research is very important, and this can only be accomplished with international collaboration. If the executive committee includes representatives from international regulatory groups and funding agencies, industry, and members of the global clinical trials network(s) chosen to develop the protocol and carry out the research, it may be possible to achieve international agreement more rapidly on issues that have often led to lengthy delays.

Below are examples of issues that often take considerable time to resolve:

- While NIH requires that multi-center clinical trials use a central IRB for the U.S. sites, many U.S. sites require a signed contract, and a local IRB approval for issues that relate to data confidentiality, and the handling of specimens for participants with infectious diseases. All sites should have pre-existing reliance agreements with the central IRB. Streamlined human subjects use reviews should be required when emergency medical research is involved.
- Many international sites require material transfer agreements for stored specimens that are restrictive in terms of use; some require re-consenting participants. In some countries, sites cannot collect specimens for genomics research or must store specimens locally. As part of conducting trials, biological samples are collected for analysis. During epidemics, analyses are time sensitive as data from clinical trials are used to study the infectious pathogen and disease pathophysiology. Seamless transfer of such samples to a central biorepository is hence essential.
- Confidentiality and privacy rules, e.g., HIPAA in the U.S. and General Data Protection Regulations (GDPR) in the European Union, have added to the costs and liability of exporting data from sites to a central data management and statistical center- these must be streamlined.
- Requirements for indemnification and insurance by sites in some countries outside of the U.S. for NIH-funded research add to trial costs and increase the time for a site to initiate the trial- these must be streamlined as well.

5. Identifying viable technical strategies for data capture

Simple to use, reliable methods for collection of data in a multi-site clinical trial during a disease outbreak or other emergency are critical to the rapid start-up and ultimate success of the trial.

Since this will be addressed by a separate RFI, we limit our comments to one strategy, which is under study, and comment on other strategies we have considered for use in international clinical trials.

- The capture of data from electronic health records (EHR) for use in clinical research is a rapidly expanding area, as witnessed by the latest technical advances in the Fast Healthcare Interoperability Resources (FHIR) specification and implementation. [19] Results thus far have been mixed. Capturing data from the EHR, particularly laboratory and vital signs, has been shown to reduce data entry errors and can reduce the amount of time spent on data entry by research coordinators. However, not all data collected in the context of trials is routinely available in the EHR. More importantly, different specifications of the EHR and data security and privacy controls across sites would likely require each site's information technology and informatics teams to build site specific tools to capture EHR data rather than developing a single, centrally administered tool. The further development of these tools may be possible during "warm base" trials.
- Regulatory issues around consent are complex; however, we have had success with centralized creation of sample consent forms and allowing sites to tailor the content. While central management of consent may sound appealing, attempts to do this will need to navigate the regulatory complexities of every participating site. The use of a centrally managed eConsent process faces not only site-specific regulatory challenges but also needs to navigate the IT requirements of all sites. Our experience has been that IT departments at sites develop their own requirements, and these are even less uniform than requirements enforced by site specific IRBs. These IT requirements also cover sharing of electronic data, especially protected health information.
- Use of REDCap, a widely used electronic case report form (eCRF) system, housed at a single data center makes data collection and quality control simple and reliable. We have found that using a quality control system that examines incoming data for likely errors and generates daily

report for the sites contributing the likely errors is essential for maintaining high quality data. These reports detail specific potential errors or missing data which study coordinators at the sites can work to resolve in a timely manner. These systems are simple to setup and maintain and can be rapidly validated and deployed in an emergency setting.

- The use of a centralized data repository that is closely integrated with the systems at the SDMC facilitates rapid study start-up and analysis of biospecimens. The eCRFs capture identifiers for specimens which are then shipped to a centralized location in the U.S. Information about specimens is then collected in databases which are mirrored at the SDMC. This allows for rapid determination of specimens which satisfy specific clinical criteria for evaluation by specialized assays. These processes have been essential to our use of novel assays and the insights they provide in the study of emerging diseases.
- Site staff are trained on data collection and study procedures prior to study start. With the use of a master protocol, initial training requires more time and would be best done as part of "warm base" research. Training for subsequent protocols (developed in response to an outbreak or other emergency) is rapid and materials are available on a website. Our studies have benefitted from centralized training on study procedures and data collection by staff at the data center since these staff are highly knowledgeable about the data collection systems.

6. **International coordination and capacity**

The 2022 World Health Assembly resolution 75.8 (16.2) on strengthening of clinical trials noted that "*clinical trials on new health interventions are likely to produce the clearest result when carried out in diverse settings, including all major population groups the intervention is intended to benefit, with a particular focus on under-represented populations*".

Developing, fostering, and strengthening new and existing research infrastructure, especially in LMICs, is crucial in establishing an expeditious, efficient, and coordinated response to global emerging diseases. This will ensure representation of a diverse population, allow trials to follow pandemic waves as they spread geographically, and strengthen generalizability, acceptance of trial findings, and scientific rigor in the trials conducted.

A decentralized organization with multiple international coordinating centers such as described above (introduction and section 1 and 2) ensures detailed understanding of local and regional circumstances and helps identify new international sites and collaborating national research networks. The identification of new sites takes time, but with this approach the number of international sites can be continuously expanded in different geographic regions.

Through mentoring and inclusion of more junior members from different geographical settings in the design and reporting of results of trials, principles of global diversity and equity are realized. A meaningful commitment to investing back into people capacity at international sites, particularly in LMICs, is consistent with pledges for capacity building from both QUAD leaders and G7. A transparent and inclusive policy on participation from all sites in academic output is an important part of building international relationships and an environment of collective ownership of a clinical trial. Global equity can only be achieved though meaningful involvement in all stages of the development of studies, including from their initial concepts.

The challenges posed by lack of a common international regulatory body, differing regulatory requirements of each country, difficulty in drug labelling including translation requirements and drug shipping to various countries are significant. The staggered regulatory approval process whereby approval at U.S. FDA level is required prior to submission at other locations leads to delays in activating international sites. Such processes hamper the desired agile and flexible

deployment of novel clinical trials, especially if an initial transmission focus of an epidemic with pandemic potential is in a non-U.S. region.

As mentioned in our response to section 1, an executive committee that includes representation from international regulatory groups and government organizations as part of an overall governance structure is considered necessary to ensure rapid international trial implementation during a public health emergency.

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References:

1. The INSIGHT START Study Group. Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection. New England Journal of Medicine 2015;373(9):795-807. DOI: 10.1056/NEJMoa1506816.
2. The INSIGHT–ESPRIT Study Group and SILCAAT Scientific Committee. Interleukin-2 Therapy in Patients with HIV Infection. New England Journal of Medicine 2009;361(16):1548-1559. DOI: 10.1056/NEJMoa0903175.
3. The Strategies for Management of Antiretroviral Therapy (SMART) Study Group. CD4+ Count–Guided Interruption of Antiretroviral Treatment. New England Journal of Medicine 2006;355(22):2283-2296. DOI: 10.1056/NEJMoa062360.
4. Lynfield R, Davey R, Dwyer DE, et al. Outcomes of Influenza A(H1N1)pdm09 Virus Infection: Results from Two International Cohort Studies. PLOS ONE 2014;9(7):e101785. DOI: 10.1371/journal.pone.0101785.
5. Peloso GM, Tcheandjieu C, McGeary JE, et al. Genetic Loci Associated With COVID-19 Positivity and Hospitalization in White, Black, and Hispanic Veterans of the VA Million Veteran Program. Front Genet 2021;12:777076. (In eng). DOI: 10.3389/fgene.2021.777076.
6. Lee GC, Restrepo MI, Harper N, et al. Immunologic resilience and COVID-19 survival advantage. Journal of Allergy and Clinical Immunology 2021;148(5):1176-1191. https://doi.org/10.1016/j.jaci.2021.08.021.
7. Moskowitz A, Shotwell MS, Gibbs KW, et al. Oxygen-Free Days as an Outcome Measure in Clinical Trials of Therapies for COVID-19 and Other Causes of New-Onset Hypoxemia. Chest 2022;162(4):804-814. DOI: https://doi.org/10.1016/j.chest.2022.04.145.
8. Bowdish ME, Barkauskas CE, Overbey JR, et al. A Randomized Trial of Mesenchymal Stromal Cells for Moderate to Severe ARDS From COVID-19. American Journal of Respiratory and Critical Care Medicine;0(ja):null. DOI: 10.1164/rccm.202201-0157OC.
9. Self WH, Semler MW, Leither LM, et al. Effect of Hydroxychloroquine on Clinical Status at 14 Days in Hospitalized Patients With COVID-19: A Randomized Clinical Trial. Jama 2020;324(21):2165-2176. (In eng). DOI: 10.1001/jama.2020.22240.
10. ACTIV-3/Therapeutics for Inpatients with COVID-19 (TICO) Study Group. Monoclonal Antibody for Patients with Covid-19. New England Journal of Medicine 2021;384(12):1170-1171. DOI: 10.1056/NEJMc2100221.
11. ACTIV-3/TICO Study Group. Efficacy and Safety of Ensovibep for Adults Hospitalized With COVID-19. Annals of Internal Medicine 2022;175(9):1266-1274. DOI: 10.7326/M22-1503.

12. Holland TL, Ginde AA, Paredes R, et al. Tixagevimab–cilgavimab for treatment of patients hospitalised with COVID-19: a randomised, double-blind, phase 3 trial. The Lancet Respiratory Medicine 2022;10(10):972-984. https://doi.org/10.1016/S2213-2600(22)00215-6.
13. Self WH, Sandkovsky U, Reilly CS, et al. Efficacy and safety of two neutralising monoclonal antibody therapies, sotrovimab and BRII-196 plus BRII-198, for adults hospitalised with COVID-19 (TICO): a randomised controlled trial. The Lancet Infectious Diseases 2022;22(5):622-635. https://doi.org/10.1016/S1473-3099(21)00751-9.
14. ITAC (INSIGHT 013) Study Group. Hyperimmune immunoglobulin for hospitalised patients with COVID-19 (ITAC): a double-blind, placebo-controlled, phase 3, randomised trial. Lancet 2022;399(10324):530-540. (In eng). DOI: 10.1016/s0140-6736(22)00101-5.
15. Ader F, Bouscambert-Duchamp M, Hites M, et al. Remdesivir plus standard of care versus standard of care alone for the treatment of patients admitted to hospital with COVID-19 (DisCoVeRy): a phase 3, randomised, controlled, open-label trial. Lancet Infect Dis 2022;22(2):209-221. (In eng). DOI: 10.1016/s1473-3099(21)00485-0.
16. Ader F, Peiffer-Smadja N, Poissy J, et al. An open-label randomized controlled trial of the effect of lopinavir/ritonavir, lopinavir/ritonavir plus IFN-β-1a and hydroxychloroquine in hospitalized patients with COVID-19. Clin Microbiol Infect 2021;27(12):1826-1837. (In eng). DOI: 10.1016/j.cmi.2021.05.020.
17. Davey RT, Jr., Dodd L, Proschan MA, et al. A Randomized, Controlled Trial of ZMapp for Ebola Virus Infection. N Engl J Med 2016;375(15):1448-1456. (In eng). DOI: 10.1056/NEJMoa1604330.
18. Kieh M, Richert L, Beavogui AH, et al. Randomized Trial of Vaccines for Zaire Ebola Virus Disease. N Engl J Med 2022;387(26):2411-2424. (In eng). DOI: 10.1056/NEJMoa2200072.
19. Cheng AC, Banasiewicz MK, Johnson JD, et al. Evaluating Automated Electronic Case Report Form Data Entry from Electronic Health Records. Journal of Clinical and Translational Science 2022:1-18. DOI: 10.1017/cts.2022.514.

January 27, 2023

The Honorable Arati Prabhakar
Director
Office of Science and Technology Policy
Executive Office of the President
1650 Pennsylvania Ave., NW
Washington, DC 20504

Submitted electronically to emergencyclinicaltrials@ostp.eop.gov

Dear Dr. Prabhakar,

This letter is in response to the Office of Science and Technology Policy's (OSTP) Request for Information; Clinical Research Infrastructure and Emergency Clinical Trials dated October 26, 2022 and as extended on November 22, 2022.

Vir Biotechnology is a commercial-stage immunology company focused on combining immunologic insights with cutting-edge technologies to treat and prevent serious infectious diseases. Vir has assembled four technology platforms that are designed to stimulate and enhance the immune system including our industry-leading antibody platform that resulted in the co-discovery of ansumvimab-zykl for the treatment of Ebola and the discovery and development of sotrovimab for the treatment of COVID-19. As part of ongoing efforts to bolster pandemic preparedness, Vir is partnering with BARDA to advance an investigational monoclonal antibody for use as pre-exposure prophylaxis for influenza A infection.

Vir applauds OSTP's and the National Security Council's continued focus through the American Pandemic Preparedness Plan and the National Biodefense Strategy to be forward leaning on having an effective plan and response in place and believe that support for expedited clinical development of safe and effective treatments is an essential component towards that end. We would suggest that in order to achieve success in expedited and accelerated development of therapies, such a pandemic plan must ensure alignment of federal agencies – and ideally with ex-US regulatory and policy making institutions – with a key objective – to provide clear regulatory guidance and expectations. Proactive implementation of regulatory expectations and guidance should occur during non-pandemic times to create readiness to ensure public and private sectors are well versed in development pathways for assets that may become essential in emergency settings. Subsequently, proactive implementation of a clinical development structure that meets the aligned regulatory needs will permit the rapid conduct of clinical trials nationally and globally – a critical factor in being able to quickly contain a pandemic.

Given the excellent work across multiple federal agencies to assess pathogens of pandemic potential and the pathogen families of greatest concern, we would also suggest the contemplation of revising and editing guidance documents for the COVID-19 pandemic to apply to these known classes of concerning pathogens. At a minimum, we would recommend that the Food and Drug Administration convene a meeting of interested stakeholders to begin a dialogue on clinical development processes that developers would be expected to follow for the viral families of highest concern.

CONSIDERATIONS ON GOVERNANCE

As mentioned above, proactive robust regulatory guidance in expectations and development pathways for potential pandemic pathogens will be crucial to rapidly respond in an emergency situation with the aim of minimizing product development timelines. As it relates to any potential governance structure for emergency clinical trials that might be proposed, we would ask you keep these considerations in mind:

- Ensuring representation from both the public and private sectors, large pharmaceutical and small biotech companies, and key opinion leaders across academia is critical. All entities share a common goal of prioritizing public health and can contribute through medicines, funding, academic rigor, and connections.
- The need for input and collaboration across a robust set of stakeholders is reflected in the ACTIV platform for COVID-19. One observation from the NIH-led COVID-19 ACTIV effort was that the platform protocols were predominantly developed without industry input and without consideration of sponsor requirements relative to regulatory requirements to target emergency use authorization or approval. This, in part, may be one reason for the lack of major impact from the ACTIV Clinical Trial outcomes on the regulatory labels of most, if not all, therapeutics. For the consideration of future efforts, gathering the needed diverse group of stakeholders to develop master protocols for multiple indications targeting priority pathogens of pandemic potential should be a priority. A priori discussions and consensus as well as input from relevant health authorities and guideline drafting bodies (academic and federal) can help ensure that trials are designed robustly and efficiently to minimize the time and resources required to generate the needed evidence sufficient to achieve regulatory authorization and approval and ensure provider confidence. An ancillary benefit would be to minimize unnecessary overlap and resource competition for exploratory or repurposed candidates.

CONSIDERATIONS ON CLINICAL TRIAL INFRASTRUCTURE

Having infrastructure readiness to execute trials in the event of outbreak or emergency requires timely and ongoing investment in a warm base that would be ready to execute. Protocols/operating manuals could be developed for dissemination and training. Some of these ideas were covered in the OSTP roundtables on January 11th and 12th, but we would underscore potential ideas for consideration to include:

1. ***Warm base of clinical sites***
   - Identify a network of sites with designated network and site leads committed to conducting trials during an emergency with representation from large academic institutions as well as community sites to ensure broad coverage of patients
2. ***Investment in clinical trial training***
   - Participating sites would be eligible for funding to ensure ongoing clinical trial training
   - Promote greater awareness about clinical research and its career path in order to recruit qualified personnel with appropriate credentials in training (e.g., ICH, GCP, CFR, etc.)
   - Support interstate licensure flexibility during emergencies
3. ***Support structure of service providers***
   - Enlist a network of service providers (e.g., CROs, labs, IRB/Ethic Committees) that are committed to following an agreed-upon protocol/operating manual to execute during an emergency that may diverge from institutional processes under normal operating conditions
4. ***Streamlining Service and Clinical Agreements with global considerations***
   - Emergency template of service agreements that standardize frequently negotiated sections – including but not limited to IP, publications, indemnifications
   - Better contracting infrastructure globally – Remove serial steps to enable speed. Coordination between regulator and ethical boards for parallel review and approval
   - Removing international border barriers on delivery of ancillary and clinical supplies to enable expedited study start
   - Investigator contracts and budgets – Centralized terms and payment structure
5. ***Diversifying participation in clinical trials***
   - We agree with the many comments from the January 12th OSTP roundtable on steps to improve diversity in clinical trials including engaging with trusted community leaders who have the ability to engage and educate individuals in various community settings and reduce historical distrust
   - Federal investment and support in qualified ethnic principal investigators and sites – it is Vir's experience that study participants in underserved communities expressed more trust for care providers within their own communities; however, there is a limited number of research activities conducted in these communities due to lack of resources and qualified personnel.

- Vir has experience collaborating with small minority-owned providers, large national platforms such as Black Health Matters, and various disease advocacy groups who have intimate relationships to enable trusted in-person and digital outreach. Our Phase III COMET-ICE SARS-CoV-2 early treatment trial had 70 percent representation from Latinx and Black populations, whom COVID-19 has severely impacted.

CONSIDERATIONS ON INTERNATIONAL COORDINATION AND CAPACITY

Most outbreaks originate in low- and middle-income countries. The ability to contain such outbreaks before they become pandemics will be contingent upon being able to rapidly intervene in such settings. Accordingly, the clinical trial infrastructure – from operations to supply chain – needs to be cultivated globally as well as domestically. As it relates to any potential international coordination and capacity for emergency clinical trials that might be proposed, we would ask you keep these considerations in mind:

- Encourage the USG when working with international partners and negotiating international agreements to focus on harmonizing as many regulations as possible. As two examples, some countries require an ethics committee approval before clinical trial contract execution and some countries require wet-ink signatures instead of electronic signatures.
- Encourage the adoption of a standard, global label (i.e., an English-only label on IP) to enable flexible supplies globally to significantly reduce country timelines. With the dynamic nature of a global pandemic, one of the biggest challenges is ramping up to match the pandemic where it ebbs and flows. From a drug-supply perspective, this can be challenging to accommodate as every country has its own clinical trial IP labeling requirements (e.g., expiry dates on labels, special cautionary statements, and local label translations). Local translations and preparation material could be provided via supplemental documents (e.g., pharmacy manual).
- Allow for importation to occur concurrently with clinical trial application submissions. Doing so would reduce study start-up lead times by removing drug importation as a bottle neck. Drug importation (e.g., import licenses) for many countries (Latin America, South Africa) is gated by health authority approval of the study thus stalling moving clinical trial material into local country depots. For the US, it would mean allowing for importation into the US once the IND has been submitted (within the 30-day window prior to IND approval) rather than waiting for actual IND approval.
- For any commercial drugs that are required for the trial, government support in working with the market authorization holder to obtain rapid access to supply and documentation is required. There is potential that an investigational drug could be used in combination with another commercially approved drug or in comparison with a drug under emergency use authorization and speedy and unfettered access to those drugs to support emergency clinical trials would be key.

- Encourage central reserve of essential clinical supplies and equipment to ensure rapid distribution to clinical site networks during emergency. As two examples, saline and IV pumps were in short supply leading to lengthy delays during the COVID-19 pandemic.
- Enable maximum access to genetic sequences and biospecimens – which could lead to future development of medical countermeasures to be tested in clinical trials -- in any upcoming global pandemic preparedness negotiations.

While there are different models and approaches to be considered in developing a pre-established clinical trial infrastructure, we want to reiterate our belief that success is contingent on proactive alignment with FDA and other applicable regulators that clinical data generated through emergency trials will be sufficiently robust to support regulatory approvals or authorizations prior to implementation of any pivotal studies.

We value this opportunity to provide comments. If you have questions or would like additional information, please contact Douglas Stoss, Vice President of Policy and Government Affairs at dstoss@vir.bio.

Request for Information; Clinical Research Infrastructure and Emergency Clinical Trials

January 27, 2023

By Electronic Submission

Office of Science and Technology Policy
Eisenhower Executive Office Building
1650 Pennsylvania Avenue
Washington, DC 20504

RE: Document No. 2022-23110 Emergency Clinical Trials RFI

Regeneron has unique experience conducting emergency trials, starting early in the COVID-19 pandemic. We engaged with sites, patients, trial networks, and industry partners to apply best practices. This included clinical trials for an existing IL-6R antibody, commencing in March 2020, and successful development of casirivimab-imdevimab (REGEN-COV), commencing in June 2020, leading to an FDA EUA in January 2021. Also, Regeneron's antibody cocktail REGN-EB3 (Inmazeb) became the first FDA-approved treatment for Ebola in October 2020.

The RFI requested comment on several important areas. However, there are additional critical challenges and complexities we have encountered in real-world emergency trial experience. We invite federal team members to an interactive discussion with our scientific and operational experts, particularly to share critical Regeneron learnings from the ACTIV trials and RECOVERY trials.

We have focused on the RFI topics of identifying research institutions and building diversity and equity; warm-base research; and emergency master agreements. We submit these comments and recommendations to help ensure that coordinated and large-scale clinical trials can be efficiently carried out across a range of more diverse patients and sites to address outbreaks of disease and other emergencies.

Regeneron invents life-transforming medicines for people with serious diseases. Founded and led for 30 years by physician-scientists, our unique ability to repeatedly and consistently translate science into medicine has led to several FDA-approved treatments, most of which were homegrown in our laboratories, and numerous product candidates in development. Our approved medicines and those in our pipeline are designed to help patients with eye disease, heart disease, muscle disease, allergic and inflammatory diseases, pain, cancer, infectious diseases, and rare diseases.

Comments and Recommendations on RFI Topic Areas based on Regeneron Experience in Emergency Clinical Trials

RFI Topic	Regeneron Comments and Recommendations
Identifying and Incentivizing Research Institutions and Networks; Building Diversity and Equity	
Methods to identify sites with existing interest in or familiarity with emergency clinical trial research	**Develop a broad plan to apply data to site identification:** • Identify site locations based on **epidemiological data** and disease incidence data • Generate predictive analyses to **identify "hot spots"** where infection rates would likely increase over time • Enable early, ongoing site selection, and **include <u>experienced</u> investigators** to ensure quality and data integrity. The speed needed in a pandemic does not readily support naïve site training & coordination. **Prioritize site types** known to deliver adequate and diverse populations: • Networks of **infectious disease investigators** (e.g. CoVPN network) • Standalone **community-based research-only** sites • Academic medical centers **with enhanced research capabilities** **Start with performance-based site criteria:** prioritize sites known for fast **study start-up**; **central ethics committee** reviews; and **strong local processes for recruitment** and patient identification (e.g. via electronic health records) **Offer online protocol training**: assign study team to explain protocols, beyond just written summaries **Cultivate site/Investigator registries:** include up-to-date site performance data from study sponsors' clinical trial management systems (CTMS) and aggregators (IQVIA DQS, Informa Citeline). Enable direct updates by site staff.
Effective ways to increase diversity amongst study participants and investigators, and to expand clinical research sites into underserved areas	**Design studies for patient-centricity:** minimize in-person visits; minimize points of specimen collection as feasible, but while not compromising scientific principles of the study & data needed for evidence base. **Incorporate efforts in site selection to include underserved and vulnerable groups:** • Use census & site-level **demographic data** to ensure diverse site placement **Ensure broad outreach to increase recruitment speed, inclusion and diversity:** • Proactively set up mechanisms for **trial sponsors** to work with Federal, State and **Local agencies** to help target **physicians (investigators and referring)** and **patients** through their own websites, testing centers and to maximize any other alternative means to increase outreach • Coordinate outreach with **community groups**, and both online and "offline" e.g. **radio, retail locations** • Ensure ads, images, and language **reflect populations of interest** • Build in **peer referral** programs **Reduce the need for site visits:** • Offer options for paid transportation to sites, home specimen collection and drug administration

	• Offer patient-centric technology: eConsent; tele-visits; eCOA (electronic clinical outcomes assessments); and remote wearables & sensors; Bring Your Own Device (BYOD) options **Stipends:** Ensure stipends are offered for time and effort participating
Warm-Base Research	
Relevant disease areas for underserved and vulnerable communities	**Focus on high-risk comorbidities**: e.g. advanced age, diabetes, immunocompromised
Implementation to provide training to research-inexperienced sites, and to create a basic surge capacity	**Build a training program for naïve investigators / physicians / sites** • **Coordinate with industry, academia and community practice** • Also **upskill** experienced sites investigators to learn how to deploy DCT elements **Sponsor medical education/training:** fund educational programs for research coordinators; research pharmacists and pharmacy staff **Focus on critical thinking skills:** Up-level staff to navigate crisis situations, to deliver high quality conduct
Support as a demonstration project with commercial partnership, public-private partnership, and/or an agency-funded program	**Potential near-term demonstration with REGN14287 / next-generation COVID therapeutic in development**: • Regeneron is developing therapeutic antibodies aimed at lower resistance to future variants • Clinical trial will be initiated in 2023, pending regulatory discussions • Opportunity for non-emergency use of and feedback on new databases, talent, sites, DCT elements
Emergency Master Agreements	
Facilitating understanding and adoption	**Minimize back-and-forth**: pro-actively schedule final touchpoints for decision-makers to finalize agreements between sites and study sponsors. **Use modern rapid collaboration platforms:** e.g. for protocol feedback from regulators, IRBs, to expedite approval
Basic terms that might form part of an Emergency Master Agreement	**Focus on specificity of terms to avoid delays with vague, high-level frameworks:** • **Pre-negotiate scope of indemnification:** limit to administration of study drug and proper performance of study procedures • **Pre-specify scope of confidentiality**: include patient health information, study materials, information related to the study, and inventions • **Pre-specify patent and intellectual property rights**: define ownership not only from study inception, but also for any inventions developed during the study • **Pre-specify fair market value rates**: reduce negotiation time and improve compliance, by using protocol visit and procedure-level rates, e.g. as a prespecified percent-of-Medicare for U.S. sites

If you have any questions or additional comments, please feel free to contact our team at biodefense@groups.regeneron.com or to call us at 914-847-7000

Respectfully submitted,

Edward Cox, MD
Vice President, Regulatory Affairs
Global Development
Regeneron Pharmaceuticals, Inc.

David Weinreich, MD, MBA
Executive Vice President,
Head Global Clinical Development
Co-Head Global Development
Regeneron Pharmaceuticals, Inc.

Submitted via email to emergencyclinicaltrials@ostp.eop.gov

January 26, 2023

Stacy Murphy
Office of Science and Technology Policy
Executive Office of the President
Eisenhower Executive Office Building
1650 Pennsylvania Ave., NW
Washington, DC 20504

RE: Request for Information – Clinical Research Infrastructure and Emergency Clinical Trials

Dear Ms. Murphy,

Public Responsibility in Medicine and Research (PRIM&R) appreciates the opportunity to respond to the Request for Information – Clinical Research Infrastructure and Emergency Clinical Trials" published in the *Federal Register* on October 26, 2022.

PRIM&R is a nonprofit organization dedicated to advancing the highest ethical standards in the conduct of research. Since 1974, PRIM&R has served as a professional home and trusted thought leader for the research protections community. Through educational programming, professional development opportunities, and public policy initiatives, PRIM&R seeks to ensure that all stakeholders in the research enterprise appreciate the central importance of ethics to the advancement of science.

We recognize and appreciate the importance of proactively addressing how the research enterprise can be better prepared to respond to and efficiently conduct critical research during a public health emergency. There are lessons to be learned from the flexibility, creativity and ingenuity demonstrated by the research community in the early days of the COVID-19 pandemic. To that end, PRIM&R offers comments related to three specific areas for OSTP consideration:

1. Streamlining institutional review board (IRB) review for research during emergencies
2. Utilization of public health surveillance during emergencies
3. Tension between clinical care and research during public health emergencies.

1. Streamlining IRB review for research during emergencies

Efforts to reduce regulatory burden without undermining the safety of human subjects in such research, such as the use of reliance agreements to streamline IRB review by requiring a single IRB of record (sIRB) for multisite studies, are underway. In the RFI, OSTP requests comment "*on the possibility of developing a framework of key terms … in advance of an emergency… that can be integrated into clinical trial agreements for emergency clinical trials…"* One of the suggested key terms to be included in such an Emergency Master Agreement is the use of a sIRB.

PRIM&R notes that the use of a sIRB model may well streamline processes for study initiation and be beneficial for research conducted during emergencies. However, given that the sIRB model is relatively new, PRIM&R recommends that OSTP consider gathering evidence to determine if the sIRB model does in fact make the review process more efficient, particularly within the context of time sensitive research conducted during emergencies. For example, OSTP could consult with the Department of Health and Human Services to learn more about its exception to the sIRB requirement for COVID-related research and whether that exception was beneficial in improving the efficiency of multi-site trials during the pandemic. Adopting a flexible approach, initially, by supporting but not mandating sIRB, may provide the research community with an opportunity to learn about the most efficient pathways in future emergencies and make informed choices about the IRB review structure that can best support multisite research during an emergency.

OSTP should also consult with IRBs that have experience serving as the IRB of record for large multisite trials and gather data about experiences of IRB review during the COVID pandemic and other emergencies to learn more about models that have proven effective in both emergency and nonemergency situations and can be built into the clinical research infrastructure. Lastly, OSTP should also consider mechanisms (including funding) to ensure that research oversight systems are poised for rapid response in public health emergencies through the routine use of emergency preparedness simulation exercises.[1]

2. Utilization of public health surveillance during emergencies

There are also loopholes in the interpretation of current regulations for protecting the rights and welfare of human subjects that were highlighted during the pandemic, and which should be addressed. For example, the 2018 Federal Policy for the Protection of Human Subjects (also known as the Common Rule) deems public health surveillance activities as falling outside the regulatory definition of "research," and as such exempt from compliance with the regulatory requirements. However, the regulations do not clearly distinguish between public health activities that constitute *surveillance* and those that

[1] Lowe, A. E., Kraft, C., Kortepeter, M. G., Hansen, K. F., Sanger, K., Johnson, A., Grein, J. D., Martin, Julie, Rouselle, R. Garland, J.A., Spotts, J., Lowe, J. J., Sauer, L. M., Kratochvil, C. J., * Gordon, B. G. (2022). Developing a rapid response single IRB model for conducting research during a public health emergency. *Health Security, 20*(S1), S60-S70. doi:10.1089/hs.2021.0181

constitute *research.*[2] During the pandemic, IRBs saw a surge in proposals identified as "public health surveillance," where traditional protections such as informed consent and data confidentiality safeguards were therefore not triggered or required.

While PRIM&R appreciates the importance of not impeding vital public health activities, we believe that the public health surveillance exclusion must be utilized mindfully and in a manner that does not take advantage of the ambiguity in the regulations to intentionally skirt requirements such as informed consent—doing so threatens to further erode public trust in science and medicine, which may already be fragile during public health emergencies. At the same time, given that collection and future use of data is often a common part of public health surveillance activities, we acknowledge that the line between public health surveillance and research is blurry. We therefore believe that, individuals who are subjects of such activities, as well as the general public, should be given general information about the scope and purpose of any public health surveillance activities and potential future uses of data collected as part of those activities. ***PRIM&R recommends that OSTP engage the public in exploring provisions that support public health activities broadly (i.e., both surveillance and research) while ensuring that the rights and welfare of individuals and of the public at large are protected, e.g., via public service announcements/education campaigns as well as, where appropriate. informed consent, respectively. Such provisions will serve the dual purpose of sustaining public health and promoting public trust in science and medicine.***

3. Tension between clinical care and research during public health emergencies

The COVID-19 pandemic also illuminated tensions between clinical care and research during a public health emergency, specifically with reference to the use of the expanded access pathway. Expanded access (EA) to drugs that have not been approved by the Food and Drug Administration (FDA) outside clinical trials is legally permissible only if it does not interfere with drug development. During the pandemic, a large-scale expanded access program (EAP) for convalescent plasma (CCP) raised important questions about the clinical research infrastructure as well as the other real impacts of EA on clinical trials. The EAP for CCP allowed access to an unapproved product for large numbers of patients at treatment sites where the product might not otherwise have been available, perhaps because those sites were identified as not having the infrastructure to support randomized clinical trials. This was a problem, however, because data on the use of CCP in this EAP was not collected in a manner that allowed for scientifically valid assessment of CCP's safety or efficacy as a treatment for COVID-19. Moreover, the EAP was utilized at sites that did in fact have substantial research capacity: more than one-third of the top 100 NIH-funded institutions

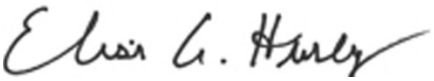
[2] Beach, M. C., Lederman, H.M., Singleton, M, Brower, R.G., Carrese, J., Ford, D. E., Hansoti, B., Hendrix, C. W., Jorgensen, E. V., Moore, R. D., Rocca, P, & Zenilman, J. M. (2020). Desperate times: Protecting the public from research without consent or oversight during public health emergencies. *Annals of Internal Medicine*, *173*(11), 926-928. doi:10.7326/M20-4631

and several hundred sites running Phase 3 COVID-19 trials, including CCP trials.[3,4] It seems likely, therefore, that at least some of the resources, including access to patients, that were invested in the EAP for CCP could just as well have been directed towards a greater number of properly designed clinical trials, which would have resulted in more rapid, robust prospective clinical data about CCP as a treatment for COVID-19.

Thus, PRIM&R recommends that OSTP urge the federal government to invest in building a better clinical infrastructure so that sites that were recruited only because of the public health emergency will be better equipped to run clinical trials under emergency and non-emergency conditions in the future, promoting clinical trial diversity and equitable access to clinical trials. In addition, there is need for a strong oversight mechanism to monitor EAPs to ensure that such programs are not utilized in a way that is detrimental to the conduct of scientifically robust clinical trials.

Thank you again for the opportunity to provide information on building a robust infrastructure that can support emergency clinical trials. We hope that our comments are useful to OSTP in this effort. PRIM&R stands ready to provide any further assistance or input that might be of use. Please feel free to contact me at 617.303.1872 or ehurley@primr.org.

Sincerely,



Elisa A. Hurley, PhD
Executive Director

cc: PRIM&R Public Policy Committee, PRIM&R Board of Directors

[3] Gustafson, M. S., Patel, A., Hong, C, Meline, M., Pena, D., Tang, C., & Lynch, H. F. (2022), Estimated clinical trial capacity of sites participating in the COVID Convalescent Plasma Expanded Access Program. *JAMA Network Open, 5*(10), e2237540. doi:10.1001/jamanetworkopen.2022.37540

[4] Sullivan, D. J., Gebo, K. A., Shoham, S., Bloch, E. M., Lau, B., Shenoy, A. G., Mosnaim, G. S., Gniadek, T. J., Fukuta, Y., Patel, B., Heath, S. L., Levine, A. C., Meisenberg, B. R., Spivak, E. S., Anjan, S., Huaman, M. A., Blair, J. E., Currier, J. S., Paxton, J. H., … Hanley, D. F. (2022). Early outpatient treatment for COVID-19 with convalescent plasma. *New England Journal of Medicine, 386*(18), 1700-11. . DOI: 10.1056/NEJMoa2119657

Comments Submitted Electronically to emergencyclinicaltrials@ostp.eop.gov

27 January 2023

Re: Request for Information: Clinical Research Infrastructure and Emergency Clinical Trials
Docket No.: 87 FR 64821; 87 FR 71368

Bayer U.S. LLC
Pharmaceuticals
100 Bayer Boulevard
Whippany, NJ 07981

301.514.3048
kim.quaintance@bayer.com

Dear Sir or Madam:

Bayer HealthCare LLC, here-in referred to as Bayer, is pleased to submit comments in response to the White House Office of Science and Technology Policy, in partnership with the National Security Council, notice of Request for Information (RFI) issued on October 26, 2022, requesting comments on clinical research infrastructure and emergency clinical trials.

Bayer is a global enterprise with core competencies in the Life Science fields of health care and agriculture with nearly 25,000 employees in 300 sites across the United States. Our products and services are designed to benefit people and improve their quality of life. At the same time, we aim to create value through innovation and are committed to the principles of sustainable development and to our social and ethical responsibilities as a corporate citizen.

Bayer is pleased to submit comments regarding clinical trials with decentralized approaches. Specifically, Bayer is providing information in relation to topics 2.b.ii: *Use of decentralized clinical trial (DCT) design elements, or other innovative approaches such as trials conducted at the point of care* and 2.b.iii. *Use of technological innovations, such as digital health technologies (DHTs), that would allow remote participation or otherwise limit the need for participants to travel* detailed in the RFI.

Clinical trials with decentralized features have the potential to improve clinical trial access by engaging more people in research, increasing trial opportunities for under-represented populations, and enhancing flexibility for participating in a trial for geographically remote participants and investigators, or participants who face difficulties traveling to clinical trial sites. Decentralized features could include, recruitment through a digital campaign, trial participants using a digital health technology to remotely collect data, telehealth visits, home nursing, and direct-to-patient shipment of the investigational product.

In the United States, state medical licensure disparities are limiting the ability to recruit patients from various states. In a full expression of a DCT approach sponsors of clinical trials would be able to reach a potential patient anywhere in the U.S. and enroll them into a virtual trial. However, there could be a case where a patient resides in a different state from where the clinical investigator holds their medical license, there-by posing a challenge to a full expression of a DCT approach.

Medical licensure is regulated at the state level, but investigational clinical trials and their conduct are regulated at the federal level. State licensure requirements can

place a barrier on decentralized clinical trials, as a virtual site (aka meta site) would need to have investigators on staff that are licensed in all 50 states. In response to the Covid crisis many states modified licensure requirements for health care providers, including out-of-state requirements for telehealth. Although these measures were welcomed by industry, physicians, and patients, they were temporary in nature and many states are now pulling back and starting to revoke them. To strengthen U.S. capacity for conducting clinical trials, we need to revisit state medical licensure processes currently in place and develop more permanent solutions. There are a couple of possible approaches to addressing these licensure barriers.

- Flexible reciprocity schemes, such as the Interstate Medical Licensure Compact[i], can facilitate the running of trials across multiple states. The Compact is an agreement among physicians who want to practice in multiple states. The mission of the Compact is to increase access to health care, particularity in underserved and rural areas.

- Another approach that could have a positive impact includes federal and state legislation that would differentiate the practice of medicine and clinical trials. For example, limited waivers could be created for clinical trials.

- Finally, federal and state legislation that would ease or remove these licensure barriers could be another approach. Federal legislation, such as the Equal Access to Care Act[ii], introduced in response to the Covid crisis to provide for a broader application of telehealth visits, may be a decent model to build on that provides for telehealth across state lines.

In conclusion, we thank you for your consideration of these comments. If you have any questions or would like to discuss these comments further, please do not hesitate to contact me by phone at 301.514.3048 or via e-mail at kim.quaintance@bayer.com.

Sincerely,

Kim Quaintance-Lunn,
Vice President, US Regulatory Lead
Regulatory Affairs

[i] *The Interstate Medical Licensure Compact is an agreement among participating U.S. states to work together to significantly streamline the licensing process for physicians who want to practice in multiple states. It offers a voluntary, expedited pathway to licensure for physicians who qualify.*
[ii] Text - H.R.688 - 117th Congress (2021-2022): Equal Access to Care Act | Congress.gov | Library of Congress

DATAVANT

44 Montgomery St, 3rd Floor ♦ San Francisco, CA 94104

Request for Information; Clinical Research Infrastructure and Emergency Clinical Trials
Office of Science and Technology Policy (OSTP)
submitted via email emergencyclinicaltrials@ostp.eop.gov

Organization: Datavant, Inc.
Respondent Type: Industry
Contact: Doug Fridsma, CMIO, doug@datavant.com

Organizational Details: Datavant is the leader in privacy preserving data exchange, working with over 500 institutions to connect health data. Our mission is to connect the world's health data to improve patient outcomes and bring new treatments to patients faster. To accomplish this, we are connecting a network of companies, non-profits, and government entities that utilize our common infrastructure for the safe exchange of patient-level health information.

At Datavant, we believe that data fragmentation is the largest challenge facing the health data industry, and protecting patient privacy is paramount when using health data to improve health and health care. We are focused on building an open data ecosystem that allows stakeholders in the healthcare system to freely exchange data while protecting patient privacy.

Datavant has extensive experience in supporting clinical research infrastructure for both consented clinical trials that use (identifiable data and for clinical studies that use privacy-enhanced de-identified data.

- Extensive record retrieval capabilities to support life sciences clinical research
- Support low cost phase 4 clinical studies through consented tokenization of clinical trial participant data and aggregate de-identified data
- Privacy-preserving record linkage (PPRL) technology to enable disparate records to be linked in a de-identified manner,
- Data de-identification and redaction tools and services, which enable data to be redacted and modified to meet the definition of de-identification within HIPAA,
- HIPAA Expert Determination and data risk disclosure tools and services, applying statistical and cryptographic expertise to ensure datasets formulated meet the definition of the HIPAA Privacy Rule for the Expert Determination Standard §164.514(b)(1).

Datavant's extensive experience in robust, comprehensive record retrieval provides digital and manual retrieval services for a complete view of a patient's medical record for patient care and consented clinical trials research.

In addition, Datavant's privacy-preserving record linkage and de-identification technology is a foundational, neutral privacy enhancing technology. It has been used to power innovative solutions that enable scientific advancement while preserving individual privacy. The use cases that this technology powers includes, but is not limited to:

- The formation of registries and data collaboratives such as the NIH National COVID Cohort Collaborative, N3C.
- Linkages between trial data and real world data sources (e.g. claims, EHR data) to form more complete longitudinal views of clinical trial cohorts for long term safety and effectiveness studies.
- Discovery of shared patient cohorts across disparate datasets to form more complete longitudinal medical records for patient cohorts of interest.
- Real World Data repositories to power large scale evidence generation studies.
- Linkages between data sources that fall under differing privacy frameworks such as health data and social determinants of health data.

We draw on our experience across all these various use cases in response to this request for information regarding advancing privacy-enhancing technologies. In this response, we have focused on questions regarding the Emergency Master Agreement. Additional details on clinical data have been provided in responses to the the second RFI.

Emergency Master Agreements should consider using PPRL methods to accelerate the use of RWD

Our experience in FDA and NIH sponsored research suggests that master data use agreements can be the most significant barrier to rapid initiation of clinical research projects. Efforts to develop standardized, pre-signed agreements for emergency clinical trials is one of the most effective means to accelerate emergency clinical research.

To accelerate emergency clinical trials, Master agreements need to be established BEFORE a pandemic or other emergency, and updated with the specific data and requirements that a particular clinical trial will require. While clinical trials will require consent for participation, if real world data has been properly de-identified and consent for the use of de-identified data and linkages is obtained, there can be potentially life-saving benefits.

We have direct experience in using PPRL in emergency clinical trials. A vaccine developer consented participants in a vaccine clinical trial to have their data tokenized and de-identified as part of their ongoing study. This proved to be fortuitous when an unexpected concern about cardiac arrhythmias associated with vaccination was raised. Using the de-identified tokens, they were able to rapidly identify past medical records for

these patients, and link them to current study day and follow through. Rather than stop the trial or repeat it with specific questions related to cardiac arrhythmias, the investigators were able to identify previously unknown pre-existing conditions that explained the concern, and they were able to continue the trials without interruption. In emergency clinical trials, it is not always possible to know all possible questions to ask or past-medical history that may be relevant. Using PPRL tokens, we were able to accelerate the completion of the clinical trial, and prevent delays.

We have extensive experience with using de-identified data to support site selection, to create synthetic, non-duplicative controls, and to accelerate post-marketing surveillance. These capabilities should be part of the Master Emergency Use agreement, and provide a mechanism to both accelerate trial initiation and to rapidly address new concerns that may arise in the trial with the application of linked RWD.

We recommend that in addition to the usual elements in a Master Emergency use agreement, we recommend that these agreements include elements necessary to use linked RWD in the clinical studies. This would include 1) the use of de-identified data to support pre-trial set up and site selection 2) consent for tokenization and linking during and after the study completion,3) using RWD to augment study data, and 4) the use of de-identified, linked data for phase 4 safety and post-marketing monitoring. With these capabilities in place prior to the need for an emergency trial, all phases of the clinical trial can benefit.

We are appreciative of the opportunity to comment on this RFI, and look forward to supporting the ongoing need for better emergency clinical trials infrastructure.

Sincerely,

Douglas B Fridsma, MD, PhD
Chief Medical Informatics Officer
Datavant

This response is on behalf of 1Day Sooner, an advocacy nonprofit that works towards accelerating vaccine development by advocating for an expanded use of challenge studies and innovative regulatory and financial structures like advance market commitments. 1Day Sooner was founded at the beginning of the COVID-19 pandemic to represent volunteers for COVID-19 challenge trials, and continues to advocate for challenge volunteers who want to participate in high-risk, high-reward medical studies. For further information, please visit 1daysooner.org.

Responses to Information Requested

Response to 3.a.i. We are of the opinion that disease areas that are most relevant to communities and would benefit most from being the target of "warm base" clinical research are respiratory diseases, particularly of the coronavirus family, which have demonstrated particular susceptibility to becoming epidemics over the past thirty years. The COVID-19 pandemic has exposed the fragility of the U.S. healthcare system, with underserved communities being disproportionately exposed to higher risks of severe disease and death. This is unsurprising, with health disparities being more commonly associated with respiratory diseases. Honing the U.S. 's capabilities for swiftly bringing to market medical countermeasures (vaccines in particular) against respiratory diseases, should therefore be a top priority. Not only would such countermeasures help mitigate the evolution of respiratory viruses into potential epidemics by restricting viral mutation, but would also serve as prototypes to aid rapid development of medical countermeasures in response to future respiratory outbreaks from the same viral family.

Response to 3.a.ii: As described in the supplementary material attached to this Request for Information, a "warm base" of clinical research capacity would ensure that trial sites are in a state of readiness to undertake additional or future research in response to an outbreak or other emergency.

In accordance with this definition, we are of the opinion that infectious diseases, as opposed to other conditions such as cancer, heart disease, or rare disease, should be the primary target for "warm base" clinical research. This is due to infectious diseases being the most likely cause for scaling a "warm base," and thus intermediary research ought to reflect this.

Response to 3.c. We are of the opinion that a joint public-private partnership would serve as the best model for supporting "warm base" research. Operation Warp Speed, the $18 billion public-private program to accelerate COVID-19 vaccines in the US, offers an excellent example of the advantages of leveraging existing industry expertise in support of government programs, including setting up large-scale human clinical trials at speed.

We are also of the opinion that an agency-funded program could appropriately support "warm base" research. Our view is informed by the success of the Clinical Trial Capacity Working Group within NIH's Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV). This working group was established in response to the COVID-19 pandemic in order to support the scaling of clinical trial sites for COVID-19 vaccines. To this effect, it developed an inventory of clinical trial capacity, including networks from NIH Institutes and Centres and contract research organizations, that were potential settings for conducting COVID-19 clinical trials.

Response to 3. more broadly. We are of the opinion that a "warm base" for clinical trials ought to encompass patient recruitment. Successful recruitment of patients is one of the most challenging aspects in conducting clinical trials and would therefore benefit from involvement within "warm base" activities. Globally, more than 80% of trials fail to enroll on time, requiring an extension of study and or addition of new study sites. A research participant corps, where recruitment would be targeted toward highly motivated, well-educated, and pro-social individuals—mirroring those who signed up with 1Day Sooner in 2020 to volunteer for COVID-19 challenge studies in 2020—and prioritize the robust representation of underrepresented minority groups, could be a highly advantageous feature of the proposed "warm base" model. Such a corps could address the potential safety issues associated with accelerated entry into early phase studies. Before entering the corps, individuals would undergo basic medical screening to confirm they are not obviously ineligible for Phase I trials and challenge studies due to an existing medical condition, and receive information about behavior that may disqualify them from certain trials (such as donating blood within eight weeks before Day 1 of the trial). While they would need additional screening before entering a specific trial, the initial screening would cut down on the number of rejections from the trial-specific screening.

The NIH currently funds ResearchMatch, a registry that connects people who are trying to find research studies, and researchers seeking people to participate in their studies. This initiative would be a natural extension of this effort.

Response to 3. more broadly. We are of the opinion that including human challenge trials within the "warm base" model for clinical trials would be highly advantageous. Human challenge trials lend themselves incredibly well to outbreaks and public health emergencies, since they are in principle faster than normal field trials and require less participants. Furthermore, challenge trials allow researchers unique insight about a virus that would inform developments of future vaccines and treatments. This includes the pathogenesis of a virus, the role of certain antibodies, the discovery of particular biomarkers to indicate a vaccine's efficacy, and the potential of viral shedding.

Response to Request for Information (RFI) on Clinical Research Infrastructure and Emergency Clinical Trials

Jennifer Sculley, MDes, McKinley Sherrod, MDes, Lynn B. Gerald, PhD, MSPH, Hugh Musick, MBA, Lauren Castro, APN, Jerry Krishnan, MD, PhD, Population Health Sciences Program, University of Illinois Chicago (UIC).

Stakeholder type: research institution

Submitted: 1/27/2023

RECOMMENDATIONS BASED ON EXPERIENCE FROM FOUR PROJECTS IN ACUTE AND POST-ACUTE COVID

In response to Request for Information (RFI) on Clinical Research Infrastructure and Emergency Clinical Trials (87 FR 64821), UIC offers our experiences and lessons learned during the following studies:

- **NIH/NHLBI ACTIV-4B** (PI: Frank C Sciurba, Paul Ridker, Jean Connors, Jerry Krishnan, Steve Wisniewski, NCT04498273, 8/2020-2/2022)
- **NIH/NHLBI ACTIV-4C** (PI: Thomas L. Ortel, Tracy Wang, Jerry Krishnan, Steve Wisniewski, NCT04650087, 12/2020-11/2022)
- **NIH/NHLBI RE-CONNECTs** (PI: Jerry Krishnan, Sonia Thomas, 1OT2HL156812-01, 12/31/21-6/10/22)
- **NIH RECOVER** (PIs: Stuart Katz, Leora Horwitz, Andrea Troxel, NCT05172024, 12/2021-present); ILLInet RECOVER Hub (PI: Jerry Krishnan)

RESPONSE TO INFORMATION REQUESTED

1. **GOVERNANCE FOR EMERGENCY CLINICAL TRIALS RESPONSE**

g. **Best practices, including "quality by design" principles, for designing trials so that they capture the data needed without unnecessary complexity that can complicate execution.**

Comment: While elegant scientific study designs are important for reducing complexity and streamlining execution, we've observed that significant difficulty can arise from under-supported study management and from overlooking the human elements of study conduct, which affects recruitment and retention. We offer the following best practices to avoid these common barriers, based on our extensive experience in human-centered design, multi-center clinical trials and cohort studies, and recruitment and retention of participants traditionally under-represented in research:

Best practices for study management that reduces complexity:

- **Leverage or build working relationships:** When possible, leverage existing relationships between partners. Consistent players from study to study—including internal team members and external partners—helps to reduce ramp-up time and improve consistency of study conduct.

  When teams haven't worked together before, dedicated kick-off meeting(s) that include introductions and relationship-building for working groups and the study as a whole (even if a study has a short ramp-up period) will help to build comradery. Other kick-off activities should include discussing team norms, understanding the study organizational structure, all roles and responsibilities, and how and when decisions will be made.

  The benefits of on-going engagement with community partners is expected to accrue with the launch of the NIH CEAL Program, and should be further expanded to support greater participation by groups that typically are underrepresented in research, especially when rapid recruitment is prioritized.

- **Invest in experienced project management:** Teams should include dedicated project manager(s) with significant experience managing fast-moving, large, complex projects (distinct from the scientific team). The project manager should work closely with the study leadership team and each working group.

  Study leadership should provide clear objectives, goals, and deliverables to work groups at project onset. Working groups can then determine tactics, milestones, and timelines to provide to study leadership to gain buy-in and approval.

- **Set expectations and share how decisions will be made:** Set expectations that there are likely to be pivots; study leadership should proactively decide how to manage the communication and implementation of changes mid-stream changes to the study. However, avoid major changes when possible since mid-study changes are disruptive to study conduct. Focus on what will cause the least amount of harm and/or disruption for the participant.

  When possible, decisions should be made to promote best practices, long-term success for the study in general, and for participant management and processes (such as proactively planning to compensate participants).

- **Explicitly plan how teams will communicate:** The overall team and each working group should dedicate time to discussing how a team will function, including communication norms and channels including meetings (e.g., daily check-ins), file sharing (e.g., Box), instant messaging (e.g., Teams), expectations for team

members, processes for issue resolution. Taking time to set this infrastructure is even more essential for distributed and remote teams across multiple organizations.

Create a directory of study team members, their roles and responsibilities, and communication preferences. This should be easily accessible as a shared file, an internal webpage, or part of a shared knowledge management system like a wiki. This should be updated regularly, as staff turnover should be expected.

- **Meeting planning:** Plan for frequent meetings, especially during the start-up period or during the planning and implementation of major changes such as new recruitment pathways. This might mean meeting daily or multiple times per day.

  Make sure working group leads are included in both leadership and operational meetings. This provides high-level study context to guide the work, and helps timely information about changes and updates get to operational teams consistently.

  A directory of meetings should also be shared early including who leads, who attends, what information is shared, and what types of decisions are made. Plan how decisions, progress, and summaries should travel between meetings.

- **Meeting conduct:** A qualified project manager can lead the team forward each meeting by writing out or visually diagramming processes and plans to ensure team alignment, laying out options for decision points, and showing team progress.

- **Training + support:** Fund or recommend dedicated, centralized support for front-line staff who may be spread across institutions (e.g., lead coordinator or coordinator working group). This person should also provide robust training materials that are routinely reviewed and updated, and easy to access for staff. Training should include focus equally on the “why” as well as the “how” of the processes to promote adherence and informed decision-making.

Best practices to help studies fit participants and study staff:

- **Prioritize participants’ study experience:** To promote strong recruitment and retention, include a participant experience lead on the research team (e.g., a person with experience in user experience design, human-centered design, or related field). They should work with the protocol development team, participant representatives, and operational teams to achieve a successful experience.

- **Start with participants’ perspectives:** Plan early and ongoing access and inquiry with those representing the study population (patient advisory groups, pilot participants etc.). During the study, listening to participant calls recorded for quality and training is one way to learn what’s working and not working for participants.

At the end of studies, patient representatives can inform how participants might want to get results and be communicated with in the future.

Frontline staff are also a source of insight to the participant experience. Create relationships early and feedback loops between frontline staff and the rest of the study team. Include effort for frontline staff to help troubleshoot challenges experienced on the ground.

- **Plan for and communicate participant compensation as early as possible:** When planning a study, consider whether compensation for participants should be provided, and plan for it early so retroactive payments are not required as they consume valuable regulatory and operational staff time. Offering participant compensation is likely to promote stronger recruitment and retention. The ACTIV studies saw a 7-10% increase in retention rates following implementation of participant compensation.

- **Plan the study experience with a multi-disciplinary group including those representing potential study participants:**
  During the study planning phase, convene a session with representatives from key working groups (e.g., digital systems, data, clinicians, administration, regulatory, study coordinators, call center, patient representatives). Together, plan how the study will work, what each working group must do to support it, and what the participants' experience might be. Identify potential barriers or ways to optimize participants' experiences. Examples might include:

  Plan for different participant groups to optimize recruitment and retention: As part of an early planning session, think about different types of participants and their situations. This could be people who have different preferences (e.g., prefer online communication vs. phone communication), life circumstances (e.g., undocumented or unhoused participants), or abilities (e.g. speak only Spanish).

  Plan to fit participants' routines: Plan for and fund participant-facing coverage outside of normal business hours to accommodate participants needs (early mornings, evenings, weekends).

  Plan for warm handoffs: When participants come in contact with different team members, especially across organizations, try to provide a warm handoff for continuity and the sense that the study is all one team. This could include a direct phone transfer between study team members, or demonstrating cohesion by having a "participant profile" that includes information such as preferred names, names and ages of children, contact preferences (time, mode of contact), and notes from previous study contacts (who they talked to, when, topics of conversation).

- **Fund materials and systems that support study staff and participants in order to achieve a positive study experience for participants:**
  Funding should be allocated for the design, production, and on-demand fulfillment of print support materials (e.g., posters and brochures) and digital support materials (e.g., participant profile data, responsive call center scripts, study website, or videos) for study staff and participants. Participant-facing materials should be branded for study recognition and available in English and additional languages at the same time to promote enrolling a representative population.

  Effective support materials can help frontline staff pitch the study confidently and set expectations for what happens next. Participants can reference these materials at home and share with friends and family to enlist their support.

- **Close the study experience with respect for participants' contributions and connect to future opportunities:**

  Think about study closure early, as it can take weeks or months to implement plans at a time when staff is shifting to other projects and funds are running low. Activities could include return of results (with or without unblinding) to participants; modifying the study website to include results, or connecting participants to future research opportunities. Information may need to be in multiple languages and delivered in multiple ways (mail, phone, digital communications). This is an investment in the success of any future studies to which participants may be connected.

j. **Appropriate entities to handle projecting and tracking enrollment at study sites, monitoring the progress of clinical trials, and data management; whether existing entities could be engaged or adapted to carry out these functions for coordinated, large-scale emergency clinical trials.**

Comment: Entities responsible for data management should plan to do the following:

- **Reduce IT learning curves:** Use familiar software and systems when possible. If using new software, provide a list of features that are necessary or desired for success (e.g., live call list monitoring). Expect it will take additional time for building and testing. Lean on others who have used the software and/or hardware before to reduce the learning curve and time to production.

- **Reduce dependencies between organizations through data sharing**
  Access to real-time data is essential for conducting operations like making follow-up calls to participants, and identifying specific retention challenges. If possible, a single organization should control systems and operations that rely heavily on timely data (e.g., data and call center operations).

If this is not possible, provide direct API to those who need it. As a last resort, clearly outline team roles, processes, requirements, and turnaround time for managing changes to systems or receiving information or data (e.g. downloadable call and compensation list; daily automatic transfer to call center software).

- **Automate and use real-time data:** Leverage digital systems that support automation wherever possible. Real-time public health data can help studies target certain geographic areas at certain times to bolster recruitment (e.g., where COVID was spiking at different times).

3. **"WARM BASE" RESEARCH**

c. **How "warm base" research could best be implemented to provide training to sites that are inexperienced with clinical trial research, and to create a basic level of surge capacity at the staff level for emergency clinical trial research. We would appreciate input on other training mechanisms that could be used as well.**

Comment: Funds to support **"**warm base" research would have multiple benefits for emergency trials including experienced staffing, established infrastructure, and activated partnerships. It would support retention and professional growth of clinical trial staff, and development of infrastructure that could support both emergency and non-emergency research, including digital systems, equipment, and training (research training for community partner organizations, and cultural sensitivity training for research staff around specific populations such as Black or African American, Latino or Hispanic, undocumented populations, LGBTQ+, etc.).

Response to Emergency Clinical Trials RFI

Jan 27, 2023

Submitted to *emergencyclinicaltrials@ostp.eop.gov* from:

NHLBI Collaborating Network of Networks for Evaluating COVID-19 and Therapeutic Strategies (CONNECTS) Executive Committee, Steering Committee, and study PIs:

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Clyde Yancy, MD, MSc, Northwestern University Feinberg School of Medicine; *Steering Committee Chair*
Serpil Erzurum, MD, Cleveland Clinic; *Steering Committee Vice Chair*
Diane Nugent, MD, CHOC Children's Hospital; *Steering Committee Vice Chair*

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Background:

The NHLBI Collaborating Network of Networks for Evaluating COVID-19 and Therapeutic Strategies **(CONNECTS**) program is a component of **Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV)**. The **overarching purpose of CONNECTS** is to test host-directed interventions for COVID-19 via rapid, efficient, collaborative adaptive platform trials aimed at helping to slow or halt disease progression and speed recovery. Since 2020 CONNECTS has established a clinical trial platform spanning outpatient, in-patient (including ICU), and convalescent care. CONNECTS tested/ is testing 18 different intervention strategies in adaptive clinical trials. To date, CONNECTS has enrolled over 6,400 participants at more than 300 clinical sites both individually and as members of 20+ networks, mostly from the US, but also includes sites in Spain, Mexico, Italy, Brazil, and South Africa (**ACTIV 4a, 4b, 4c, 4 HT and C3PO**, https://nhlbi-connects.org). Unusual for clinical trials, and in response to the disparities in COVID-19 infection and mortality, approximately fifty percent of participants are from a race or ethnicity under-represented in biomedical research. Most of the patients enrolled were hospitalized for COVID-19. The **strategic approach for CONNECTS** is to fully integrate existing NHLBI networks under one organizational umbrella to ensure efficiencies; standardization; collaboration; sharing of control groups (as appropriate), resources, and data, and nimbly shift studies as needed, based on new knowledge, and changing pandemic clinical landscape following an innovative model of seamless collaboration.

Non-government members of the **CONNECTS** Steering and Executive Committees and clinical trials PIs are responding to this Request for Information on Clinical Research Infrastructure and Emergency Clinical Trials based on the combined lessons learned from these trials.

1. Governance for emergency clinical trials response.

a. Descriptions of models that could be used to establish a U.S.-level governance structure for emergency clinical trials.

- The unprecedented extent to which federal organizations worked together was beneficial. For COVID, no one group could do everything – collaboration was key.
- Critical was the ability to pull multiple research stakeholders (including NIH, FDA, CDC, and academic medical centers) to quickly brainstorm needs and ideas to address.
- Gathering multi-disciplinary experts onto teams to address specific issues relevant to the pandemic was very effective in COVID efforts: for example, the CONNECTS therapeutic agent prioritization committee, the Coagulopathy workshop in May 2020 and similar events.
- CONNECTS network-of networks model by which sites from standing NHLBI networks collaborated to design and implement trials was an effective and rapid way to convene experienced multidisciplinary researchers and implement trials more quickly than is typical.
- CONNECTS was funded through an OTA mechanism. The speed and flexibility of the funding model was effective but was still considered neither fast nor flexible enough – study teams

often were slowed by too many obstacles in decision making and internal and external approvals to make quick decisions.

b. Criteria that should be applied in determining when coordinated and potentially large-scale clinical research is needed to address an outbreak of disease or other biological incident,

- For a new emergency disease outbreak, a rapid assessment should be done to understand the state of the evidence that already exists for treatment. If there is reasonable-substantial per-existing evidence to support appropriate treatments, then focus should be on methods for rapid implementation, while evaluating for potentially more effective treatments gets started.
- We posit that, separate from infectious diseases, the US is in an emergency based on numerous wide-spread causes of declining health. Every medical research topic on leading causes of death should be thought of as an emergency, not just infectious disease pandemics. Yet the time from conception of a research idea to funding and conduct of research is far too slow, and there is minimal flexibility in the process. Systems used both to fund and to carry out clinical research must modernize through paradigm shifts. Further, even with existing efforts to study the implementation of new clinical knowledge to the bedside, clinic or community, the health care system does not adequately support knowledge translation to practice, and treatment advances take many years to be implemented and to benefit patients. The public deserves better.

c. factors relating to the outbreak or incident (*e.g.,* scope, location, severity) that should be considered in determining what types of studies are needed.

- populations disproportionately affected by the outbreak should be the primary focus of and primary participants in the clinical research.

e. Mechanisms for tracking institutions, networks and sites that might be able to participate in emergency research, to ensure adequate potential for enrollment and adequate geographic coverage, domestically and internationally.

- The CONNECTS Administrative Coordinating Center (ACC) provided a consolidated web source for tracking status of potential and contributing sites (including geographical location and overlap across CONNECTS trials). The database was continually updated. This NHLBI-level site and study hub provided efficient real-time information sharing to government and study leadership, to support rapid decision making.
- For future emergencies, such consolidated web reporting hub of potential and contributing sites for each major clinical trial across government institutions would substantially support information sharing and identify gaps and excesses on a national level. An OTA-awarded institution could be funded to maintain such a web list for future needs, seeded with site lists from the recent major COVID trials.

i. Criteria for establishing a target number and location of sites needed to support clinical trials in case of emergency.

- A Clinical trial's success relies on efficient and rapid enrollment of participants. During COVID, both the number, type, and geographical spread of enrollment sites was critical. Initially, academic sites with ongoing network studies and skilled research workforce could rapidly and adeptly shift to COVID trials in inpatient settings. Community care had access to large numbers of potential participants, but most settings needed help (which was scarce in the pandemic) to mobilize the research workforce required to perform the studies.
- Geographical spread of sites maximized enrollment as COVID peaks spread across regions. Ongoing flexible addition of new sites over the course of the trials led to visible differences in rates and diversity of the individuals enrolled. Enrollment in some studies was accelerated by the addition of international sites, where study teams could enroll large numbers during peaks of COVID infection in their region. The ability to flex across academic, community and international sites was a strength during a pandemic that spread in waves across the world and affected many communities with large differences in healthcare access.
- Future criteria for number and location of sites MUST incorporate centers that serve adults and children outside of academic research settings. The very large majority of Americans were treated in large hospitals and healthcare networks which were not incorporated in clinical trials associated with CONNECTS or any other national trials.
- Unlike COVID, pandemics do not always impact one age group more intensely than others, indeed children and newborns are frequently more vulnerable than others. Representing ~20% of US population, optimizing care and minimizing lifelong morbidity will also decrease overall healthcare costs throughout the lifespan.
- We recommend implementation of ongoing virtual infrastructure nationally encompassing large community-based hospitals, healthcare networks, and pediatric hospitals which can be readily activated with existing IRB and research templates and trained research staff to fast-track initiation of clinical trials during a pandemic. Such an infrastructure would have added value in promoting a national research core outside of emergency situations and will address current enrollment challenges outside of pandemics that are related to race, age (especially pediatrics), and socioeconomic status.

f. Procedures whereby the U.S. Government, together with external stakeholders, could oversee the development of clinical trial protocols and, where appropriate, the selection of investigational agents. It would be particularly helpful to get input on whether there is a role for public-private partnerships in this context.

- CONNECTS assembled an Agent Prioritization Committee (APC) responsible for receiving suggestions for interventional agents from government, industry, and academia. A systematic literature search of each agent was provided by the Admin Coord Center to the committee for review and prioritization in in-patient or out-patient trials depending on feasibility and potential effectiveness. The committee ultimately took this process through more than 80 interventional agents.

- A similar government-private-academic partnership is highly recommended for this purpose going forward. There were likely multiple committees focused on various approaches to COVID treatment; keeping committees organized, informed and not duplicative would be a key to success. Representation from Operation Warp Speed on these committees would be helpful to assist with rapid implementation.

g. Best practices, including "quality by design" principles, for designing trials so that they capture the data needed without unnecessary complexity that can complicate execution.

- We found that adaptive platform trials designed by multi-disciplinary expert committees with chapters for new agents added over time was remarkably efficient.
- Each protocol was developed by a team including a clinical coordinating center with collaborative lead investigators often from multiple institutions, a data coordinating center, and a single central CONNECTS laboratory and biorepository. Communication and NHLBI oversight were supported by a single CONNECTS administrative coordinating center. Information was shared across study PIs through regular CONNECTS-wide steering committees. This model allowed for standardization and harmonization of methods across CONNECTS trials. For example, when the first trial among hospital inpatients showed that the intervention might improve quality of life, the quality of life measures were expanded for subsequent inpatient trials.
- A spirit of flexibility and cooperation, and rapid building of trust among investigators who may not have been familiar with each other was critical to moving the work forward quickly.
- Groups working together to develop standards endpoints, data elements and case report forms (CRFs) was essential, yet often trailed the start of the initial trials. Standardization was required at the back end. Pre-existing libraries and collections of standardized CRFs up front would have been very helpful.
- Protocols needed to be able to change flexibly, to add or modify data items as more was learned about COVID.
- Recognizing that for COVID, post-acute sequalae became a huge public health concern, future pandemic trials should plan to measure longer term outcomes from the start (we had to add this part-way through so lost a major opportunity).
- Our unblinded trial of existing medications (ACTIV 4A) vs standard of care was much easier, faster, and cheaper to implement than a placebo-controlled trial (including less site burden) and achieved meaningful results with robust enrollment. Pros of open-label trials should be evaluated in urgent pandemic settings, with attention paid to ways to minimize bias.
- Collecting biospecimens in our trials was invaluable for provision of samples/data for important mechanistic studies. This "correlative science" that embeds mechanistic studies within the clinical trials is essential for rapidly improving the understanding of new treatments in a pandemic, because we did not know, a priori, anything about the pathophysiology of this infection. However, this needs to be balanced against the need for rapid enrollment to understand the clinical outcomes. This may be achieved by using networks of both academic and community sites with the former providing expertise in

correlative science and bandwidth for collecting biosamples and the latter being critical for enrollment without the added complication and resourcing needs of biosampling.

- Obtaining informed consent was challenging, which led to innovations such as remote consent using electronic signatures to minimize exposure of research staff to SARS-CoV2, supported, in some studies, by a centralized call center, to enroll outpatients. Further streamlining the consent process would increase efficiency. National conversations and debate on how better to integrate clinical research into clinical practice are critical.
- COVID caused staff shortages – we should expect this to occur in future emergencies and plan trials with a minimal amount of input required from clinical and study support staff.
- To encourage diversity and inclusion of CONNECTS trial participants and inclusion of sites from under-resourced hospitals, attempts were made to provide remote study coordinators to hospitals that lacked research staffing or expertise. This yielded generally poor results, as hospital onboarding was very slow, often leading to attrrition of the available coordinator.

h. Best practices for designing trials that can enroll vulnerable populations, such as the pediatric population, as needed in particular circumstances.

- Unlike Covid, pandemics do not always impact one age group more intensely than others, indeed children and newborns are frequently more vulnerable than others. Representing ~20% of US population, optimizing care and minimizing lifelong morbidity will also decrease overall healthcare costs throughout the lifespan. Clinical trials and data capture must include children, infants, and pregnant women in future emergencies.

i. Optimal ways to manage interactions with domestic and international regulatory bodies.

- It was helpful that FDA was involved with CONNECTS oversight committees, so they stayed abreast of work – an example of the unprecedented collaboration across government agencies needed to effectively respond to the COVID emergency.
- We found that FDA and IRBs prioritized pandemic research to speed up time yet did not relax criteria – this is mostly appropriate provided appropriate attention can be concurrently paid to the efficient conduct of the research. FDA did not seem to be as accepting of innovative (especially Bayesian) approaches as would have been desired, given the urgency of the pandemic setting, and the iterations required to come to an analysis plan acceptable to the FDA on some ACTIV protocols caused some unnecessary delays.
- The US and its regulatory authorities, like the FDA, needs to exert its positive influence on similar agencies in other countries through data sharing in a way to build the trust needed to allow international participation in trials. The engagement of investigators outside the US was critical to successful clinical trial enrollment in CONNECTS.

j. Appropriate entities to handle projecting and tracking enrollment at study sites, monitoring the progress of clinical trials, and data management; whether existing entities could be engaged or adapted to carry out these functions for coordinated, large-scale emergency clinical trials.

- On CONNECTS, for each trial a Data Coordinating Center (DCC) and a Clinical Coordinating Center (CCC) from research universities or not-for-profit organizations completed these tasks. The Administrative Coordinating Center (ACC) assisted NHLBI and the Steering and Executive Committees in oversight, and communication between the study leaders.
- In a large pandemic response, there is concern for capacity of DCCs and CCCs in the US. Nearly all of the top-notch organizations contributed successfully to COVID trials by shifting research priorities and staff, sharing leadership roles across multiple institutions, and/or sub-contracting components to for-profit entities. The standard NIH application, review, and award process was *substantially* sped up using the OTA mechanism. We found success of the trials was highly depended on the experience, capacity, leadership, flexibility, and innovation of awarded organizations. For future pandemic preparedness, we recommend government plans for prompt yet rigorous selection of Administrative-, Data-, and Clinical-coordinating centers for national-level trials be set in place to minimize start-up time. Pre-vetting and a standing database of such entities would be a helpful tool.
- Experienced CROs (vetted by CONNECTS leadership) were contracted by some CONNECTS trials to add sites and conduct site monitoring. We found that established CROs added capacity and CRO teams worked collaboratively, but in general CROs were much less able to act *flexibly* and their work models for collaboration and budgeting/pricing were too rigid. Flexibility is a key component of urgent pandemic research. Their cost was also substantial relative to the not-for-profit and academic sector.

2. Identifying and Incentivizing Research Institutions and Networks; Building Diversity and Equity.

b. Effective ways to increase diversity among study participants and investigators, and to expand clinical research sites into underserved areas. It would be helpful to get input on whether and how the following approaches could be useful:

- Some strategies we identified as helpful on CONNECTS to promote greater engagement of eligible individuals, which can facilitate recruitment and retention of diverse individuals as well as public support for and trust in federally funded research include:
  - Maximize optionality. Whenever possible, provide participants with choices about how they share information (e.g., on-line vs. in-person visits at home vs at a clinic)
  - Leverage studies to identify participants who can be co-enrolled into additional clinical trials. Incorporate policies and practices into studies that afford co-enrollment across trials as well as an efficient transition of participants and data from a parent study to new follow-up studies.
  - Promote transparency. Build trust and legitimacy by informing participants of how data will be used, sharing study progress, and drawing direct links between participants' contributions and scientific findings.
  - Emphasize potential "value add" to participants in recruitment and retention materials. Develop recruitment and retention strategies that center participants' opportunities to connect with peers, inform the direction of research, and learn about relevant treatment and prevention efforts.

- Prepare to refer participants to additional resources regarding questions or concerns about their symptoms. Engagement can be strengthened if the study infrastructure provides value to participants beyond activities specific to the clinical trial.

v. Leveraging the networks and community access of retail chains, including retail pharmacy chains.

- In CONNECTS ACTIV 4B outpatient trial, a CVS/retail pharmacy approach as a mechanism for patient enrollment was only modestly successful for total trial recruitment and did not substantively help with diversity and equity recruitment, nor did it substantively increase proportionate access to under-represented individuals. Reference: https://evidence.nejm.org/doi/10.1056/EVIDctcs2200149. Much more work is needed to develop retail pharmacies as part of the US research infrastructure.

e. The best ways to provide training in clinical trial practice (including regulatory requirements such as Good Clinical Practice (GCP)) where needed, targeted as appropriate to staffs' roles, including staff at sites that may not have participated in clinical trials previously.

- The readiness of clinical trial practice for emergencies must be improved. CONNECTS sites suffered from a lack of workforce in general, including research coordinator staff. Hiring and training research coordinators for a study often took months. Ideally this process should take less than 30 days. To achieve this, we require standardized national-level training of research staff. This should include the ability to rapidly recruit and/or re-deploy and train research staff across a wide range of sites, including non-academic institutions, community care sites and in diverse communities. The ability for non-clinical workforce expansion to be trained to serve as research coordinators is also a tactic to achieve emergency readiness.
- Another tactic to overcome research study workforce shortages is to create a model of virtual study coordinators that support multiple sites through quick set-up of electronic medical record online access and direct communication with teams and potentially participants located at the sites. These virtual research coordinators could support smaller sites with less research infrastructure in-place, where experienced coordinators are scarce, and where a full-time staff member is not needed. CONNECTS found that access to electronic medical records for researchers not directly employed by the institution is slow and rate-limiting. A central pool of trained, certified Study Coordinators with ability to quickly function as local staff members is critical.
- To increase diverse participation in trials, NIH must make a strong financial commitment to invest heavily in training a new generation of diverse study investigators, nurses, and coordinators at locations where they have not historically served in these roles. This takes time and cannot wait to be implemented during an emergency. One model in which some of our investigators have had moderate success in past trials is a “mentoring” site

relationship where an investigator at a highly experienced site is financially incentivized to mentor a locally affiliated site that serves a diverse patient population. Once up and running, the new site is financially incentivized to separate from the parent site as the trial progresses. By so doing, the new site is hopefully ready for subsequent trials. This is not a simple process nor is it always successful, but when it has worked, it has worked well and led to new colleagues **learning the ins and outs of operating trial sites efficiently.**

3 "Warm Base" Research.

- Collaboration of standing NHLBI-funded networks was very successful and was in fact a "warm base" research model. However, this model prepared only the experienced academic research sites for rapid inclusion in COVID trials.
- To increase research capacity at community hospitals and health centers and in locations with traditionally less research funding or infrastructure, development of further types of "warm base" networks should be evaluated. However, networks cannot be idle to be prepared – active multi-disciplinary collaborate research is necessary.
- In addition to clinical sites, "warm base" research should include active planning among clinical trial statisticians (both Bayesians and Frequentists) to develop best statistical analysis designs for clinical trials of emergency illnesses. There have been cross-collaborations amongst CONNECTS and ACTIV-wide statisticians. These conversations should continue in order to plan best statistical methods for the next emergency.

4. Emergency Master Agreement

- A well-accepted streamlined master agreement is critical. On CONNECTS, contract execution was not fast enough. At sites where this had been established, a streamlined master agreement was used https://ara4us.org/acta/about/ which greatly facilitated bringing on clinical sites. This pre-negotiated agreement is already approved by many major US academic institutions. This agreement worked well when there was not a third party (e.g., a pharmaceutical company). It would be good to have a pre-negotiated agreement suitable for when a pharma partner is involved. We need a paradigm shift in site legal negotiations to streamline master agreement completion to efficiently support all health research. Often contract negotiations take months, which stymies enrollment and un-necessarily increases research costs at a national level.
- In a pandemic research situation, contract execution and modification must be *fast and flexible* to address changes in trials in response to pandemic changes and new knowledge. The NIH OTA mechanism was implemented on CONNECTS. All funds flowed through the ACC to DCCs and CCCs and in turn to network leads and sites. From June 2020 to Dec 2022, the CONNECTS OTA was modified over 50 times. The ACC (RTI International) and each DCC/CCC provided substantial contracting and financial tracking staff. The technology and

staff needed to invoice and fund emergency trials is an important component not to be ignored. The CONNECTS OTA model worked well generally, was much faster than a usual NIH award, but was still not fast enough, slowed further by layers of sub-awards from ACC to DCC to network leads to sites.

a. Basic terms that might form part of an Emergency Master Agreement, including the following.

iii. *Use of a single IRB* across all participating trial sites. As a related point, it would be helpful to get feedback on whether an IRB should be established that is primarily devoted to emergency clinical trials.

- The CONNECTS program used existing large /experienced single IRBs for its trials. We would have significant concerns around trying to stand up a new IRB entity in an epidemic. Much preferred is to utilize existing well-functioning sIRBs. COVID research stressed the IRB systems, and there were a very limited number of experienced, large, efficient single IRBs that could handle the studies with a large number of sites. To prepare for future emergency health clinical research, we need both an increase in capacity of central national IRBs, and active emergency preparedness planning at these IRBs.
- Currently, because local site IRBs are required to approve an sIRB reliance, use of a single IRB slowed the process for initial IRB approval and study start. Once approved, the single IRB was essential to address protocol updates. However, IRB approval was again very slow each time an informed consent document was updated for a trial, as the sIRB is required to review each site-specific informed consent document. Streamlining the process of sIRB approval of informed consent documents is critical.

6. International coordination and capacity.

Designing the overall domestic emergency clinical trials effort in a way that coordinates with international clinical research efforts. It would be helpful to receive comments on how to facilitate the participation of foreign-run clinical trial networks and other foreign bodies in coordinated, large-scale emergency clinical trial protocols initiated by the U.S.

ACTIV-4a leveraged relations with existing country/region networks and international investigator to achieve aims more rapidly.

- **mpRCT**: For one ACTIV 4A study treatment, three adaptive platform trials joined together to form a multiplatform RCT. Ten countries participated. Based on prior relations, ACTIV-4a study leaders communicated with the international leaders of other open-label trials testing the same hypothesis for the same approved agent.
    - The trials underwent minor protocol modifications in order to join together at the analysis stage to form one primary analysis. Harmonizing critical aspects of the protocol and data collection **early on** was critical. This was facilitated by flexibility and agreement on key aspects such as endpoints and analytic (Bayesian) plan.

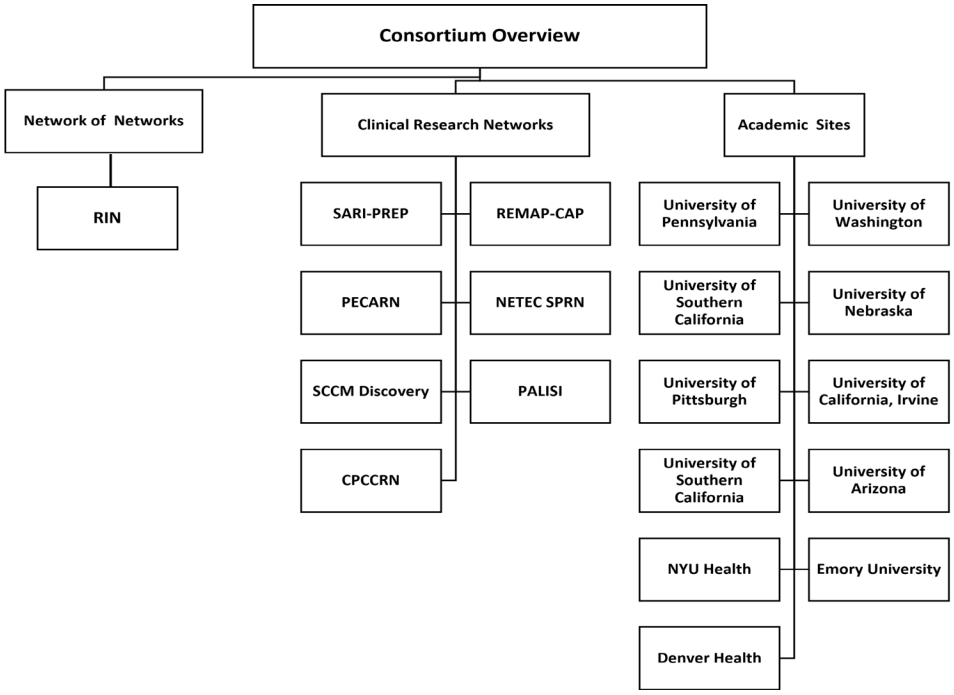
    - Data sharing for DSMB review was enabled because the same independent statistical group was doing interim analyses for DSMBs across 3 trials. Otherwise, data-sharing agreements would have incurred substantial delays.
- **Other sharing**: For some other study treatments, ACTIV 4a and similar international trials collaborated by implementing communication plans across the trials' DMSBs, including:
    - Formal sharing of data with agreed-upon SAP and stats team, with interim monitoring rules. This can be most easily done for all-cause mortality.
    - Informal sharing of interim analysis results across DSMBs to provide the most complete information for DSMB members as they consider early trial stopping.
    - Real-time data pooling across completed and ongoing trials. This was not done in ACTIV-4a but was done for NCATS-funded COMPILE study of convalescent plasma.
- **Inclusion of international sites in ACTIV 4a**: The study chair had an existing research collaboration in NHLBI trials across many countries. Four of these joined as ACTIV 4a study sites. The prior agreements and structure for collaboration needed only minor revisions.
- **ACTIV 4a general lessons learned:**
    - There should be agreements developed in advance (e.g., now) with foreign-run clinical trial networks and other foreign bodies to coordinate implementation of large-scale emergency clinical trial protocols initiated by the U.S.
    - Collaborating international networks/countries must have input into protocol development and data collection early-on. Ideally, a template protocol, analytic plan framework and CRFs should be agreed upon in advance.
    - Sponsors should have agreements established that would speed up this process for emerging illnesses.

-END-

I. Introduction and Problem Statement

Despite substantial efforts during the COVID-19 pandemic, significant gaps remain in the ability to rapidly scale up a medical countermeasure (MCM) response to public health emergencies (PHEs) in the United States.[1] The need to create and sustain vital infrastructure to rapidly conduct multicenter clinical research in emergencies is ever present as global infectious disease emergencies continue. The overarching objectives of this consortium of clinical networks are to improve outcomes during emergencies by developing and deploying mechanisms for rapid assessment of target populations for clinical trials, rapid data collection, analysis, and dissemination of findings in diverse communities. In response to this request for information (RFI), we seek to provide consolidated, collaborative recommendations supported by several experienced and productive networks including academic and community medical centers and professional societies to accomplish these goals (**Figure 1**) .

Figure 1. Consortium Overview



II. Consortium Overview

The consortium has extensive clinical trial experience, clinical expertise, and research infrastructure to accomplish the goals proposed in the RFI. The combined efforts of these sites have led to a countrywide initiative to develop a minimum data set comprehensive of multiple clinical research questions independent of patient or study type. This allows for identification of early warning signals to detect novel diseases of public health importance, peace-time strengthening of research partnerships, and the development of flexible regulatory frameworks that can be adapted rapidly in an emergency.

Severe Acute Respiratory Infection – Preparedness (SARI-PREP) is a collaboration between groups with expertise in infectious diseases, pandemic preparedness, and special pathogens, as well as with two large research consortiums that have worked together in the past to improve understanding of severe acute respiratory infection (SARI) and to disseminate that knowledge to improve patient care.[2] Key stakeholders in

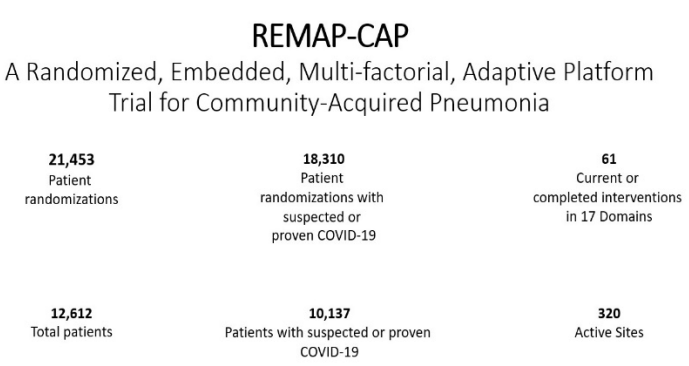
SARI-PREP include the Special Pathogens Research Network (SPRN) arm of the National Emerging Special Pathogens Training and Education Center (NETEC); the Resilience Intelligence Network (RIN); and the Society of Critical Care Medicine's (SCCM) Discovery, the Critical Care Research Network. Approved by a central institutional review board (IRB), SARI-PREP studies the clinical management of a diverse cohort of hospitalized patients with SARS-CoV-2, influenza, and other respiratory virus infections through a prospective observational study at clinical sites throughout the United States, with collection of detailed clinical data and serial collection of biologic specimens (serum, urine, upper and lower respiratory tract) for integrated multidisciplinary research to increase understanding of the pathophysiology and outcomes of patients who are severely ill from respiratory viral infections.

Resilience Intelligence Network (RIN) is a network of networks for resilience, preparedness, and response to PHEs. RIN seeks to address historical hurdles to clinical research in PHEs by convening regular meetings of all stakeholders, building shared core infrastructure, and utilizing a multiagency, all-hazards approach. This combined approach permits the conduct of high-quality, high-yield clinical research to meet immediate and long-term PHE-specific needs. This approach also fosters rapid development of consensus solutions to achieve standardization of clinical and epidemiologic data collection, real-time data and specimen analysis, rapid feedback of findings to clinicians to inform clinical management, and implementation of clinical trials that test therapeutics and other MCMs across clinical networks.

National Emerging Special Pathogens Training and Education Center (NETEC) Special Pathogens Research Network (SPRN): In response to identification of the gaps in the domestic response to the Ebola outbreak in 2014**,** the Administration for Strategic Preparedness and Response (ASPR) and the Centers for Disease Control and Prevention partnered to support development of NETEC. NETEC, in collaboration with other federal and academic partners, has established the infrastructure of the SPRN, a research network that supports rapid implementation of protocols for investigating interventions and related activities pertinent to special pathogens in both adult and pediatric patients. NETEC has established a rapid response central IRB and reliance agreements with Regional Emerging Special Pathogen Treatment Center and other special pathogen treatment centers.[3] The SPRN was active in clinical research during the COVID-19 pandemic, recruiting up to 30% of COVID-19 patients for the National Institutes of Health Adaptive COVID-19 Treatment Trials (ACTT).

Randomized, Embedded, Multi-Factorial, Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP): A key aspect of our response to the RFI is a ready-made trial platform with success enrolling patients with both moderate and severe acute respiratory failure. This platform is the U.S. region of the REMAP-CAP global trial (NCT02735707). The University of Pittsburgh Medical Center (UPMC) coordinates and manages 16 U.S. sites with enrollment on medical wards, emergency departments, and ICUs, including at UPMC, which has more than 40 hospitals. In the United States, more than 400 patients were recruited to three therapeutic domains in this COVID-19 platform trial (**Figure 2**). The U.S. REMAP-COVID

Figure 2. Recruitment statistics for REMAP-CAP, the parent global trial network to the U.S. region



platform also contributed data to the world's first multiplatform trial of anticoagulation led by our steering committee members in the Antithrombotic Therapy to Ameliorate Complications of COVID-19 (ATTACC) Network (NCT04372589). This work has been published in multiple formative trials in *JAMA* and *New England Journal of Medicine*, changing the essential treatment regimens for COVID-19.

Pediatric Acute Lung Injury and Sepsis Investigators Network (PALISI): The PALISI Network originated in 2002 to foster research to optimize the care of critically ill infants and children.[4] PALISI is unique in that its activities and meetings are funded by subscriptions from members who now comprise a multidisciplinary group of investigators from over 90 pediatric ICUs throughout the United States and Canada, with collaborations across the globe. In 2020, the network converted to a stand-alone, nonprofit 501(3)(c) structure, becoming formally independent of academic and clinical institutions or professional societies. While originally focused on acute lung injury and sepsis, the network has grown and presently has active investigations in all aspects of pediatric critical care, as represented by 15 distinct subgroups and multiple interest groups. PALISI and its related subgroups published over 350 peer-reviewed manuscripts from 2002 through September 2022.

Pediatric Emergency Care Applied Research Network (PECARN): PECARN is a multi-institutional U.S. network that conducts complex observational and interventional studies across the spectrum of pediatric emergency care. Funded through the U.S. Health Resources and Services Administration (HRSA) since 2001, PECARN conducts research into the prevention and management of acute illnesses and injuries in children. PECARN comprises six research nodes representing 18 pediatric emergency departments and six emergency medical services (EMS) agencies and one EMS node representing three EMS agencies (a total of nine EMS agencies nationally). More than 150,000 children have been enrolled in PECARN studies, leading to over 200 PECARN publications. In addition, 52 studies endorsed by PECARN have received federal funding outside of that provided by HRSA infrastructure support.

SCCM's Discovery, the Critical Care Research Network: With over 16,000 members, SCCM supports education, quality improvement, patient and family outreach, collaborative partnerships, and critical care research. Discovery fosters collaborative research to promote the advancement of science to improve outcomes for critically ill and injured patients. Since 2010, Discovery and its precursor networks have enrolled over 100,000 patients into observational and interventional trials. Discovery additionally offers services and resources to support research, including data storage, management and analysis, central IRB services, and project management.

Collaborative Pediatric Critical Care Research Network (CPCCRN): CPCCRN is a well-established network of 12 core academic clinical sites, 12 ancillary academic sites, and a data coordinating center. The network is funded by the Pediatric Trauma and Critical Illness Branch of the Eunice Kennedy Shriver National Institute of Child Health and Human Development. CPCCRN has developed an infrastructure to pursue well-designed collaborative clinical trials and meaningful descriptive studies in pediatric critical care medicine. CPCCRN's mission is to optimally manage resources and provide excellence in study design and implementation, management of regulatory documents, and management of logistical support. Through first quarter 2023, CPCCRN has completed 29 interventional or observational research trials enrolling 19,404 subjects, along with one registry. CPCCRN is currently enrolling participants for a randomized clinical trial for sepsis-induced multiple organ dysfunction in critically ill children.

III. Recommendations for RFI Areas

a. Governance for emergency clinical trials response

A public private partnership (P3) model with a governance structure that supports investment and engagement from all partners should be guided by a strategy that advances clinical research capabilities across multiple types of facilities, including academic medical institutions, emergency departments, frontline and community healthcare facilities, and outpatient centers.

A U.S. level governance structure for emergency clinical trials is critical to implementation success and outcomes. The governing body should have broad capacity to tap into critical emergency resources of the federal government while leveraging the technical and development expertise of organizations, academic medical institutions, industry, and existing networks.

A central body comprising members of the U.S. Public Health Emergency Medical Countermeasures Enterprise, cochaired by the director of the Office of Pandemic Preparedness and Response Policy and the director of the Defense Health Agency, will allow for substantive contributions across multiple federal agencies with relevant expertise. Ex officio members from representative clinical research and response networks, including the partners on this response, and industry will serve to ensure the central body is creating operational and policy solutions that can be executed effectively and identifying priority trial targets that can be implemented immediately and scaled as necessary.

The network-of-networks concept can be leveraged to support this governance structure and a series of committees that support its work. This concept was pioneered by J. Perren Cobb, MD, FACS, FCCM, of the RIN.[5] This multi-network, multi-agency, all-hazards approach permits the conduct of high-quality clinical research for broad patient populations across the care continuum to meet immediate- and long-term PHE needs, especially important for the study of pathophysiology, healthcare delivery implications, and MCMs.[6]

Guiding Principles for Prioritizing Emergency Clinical Trials	
Patient-centered, community-engaged, and equitable	Focus on saving patient lives and improving outcomes and, through community stakeholder engagement, consider the affected population's ability to access trials in their community.
Responsive and executable	Prioritize trials that can be quickly and broadly rolled out and are likely to have an impact on patient outcomes.
High-quality and scalable	Ensure that trials will be conducted in a way that will result in definitive findings, with adaptable trial designs, and that findings will be shared with the participants in a timely fashion.

Leveraging a comprehensive, nation-wide network of participating sites, pre-positioned protocols for rapid data collection for PHE response purposes could be turned on at the earliest signal identification. A series of key indicators could facilitate decisions on the types of studies needed. These indicators may include affected population information (including location, demographic information, baseline health information), epidemiologic and case count data, clinical severity and case presentation/management data, and patient management resource requirements. Development of mechanisms to rapidly assess the characteristics of a

novel SARI will help facilitate rapid and effective study design for initial interventional studies. Additional information on the capacity of the health systems in affected areas could quickly be collected using aggregate electronic health record and bed management data. Modeling an approach after the structure of the RIN, SARI-PREP, and NETEC SPRN mechanisms, a pre-emergency network of sites with a preexisting observational protocol and a central or single IRB demonstrates baseline capability to rapidly initiate clinical trials and observational human subjects research.

b. Development and maintenance of a biorepository

A critical element of governance is the management of a biorepository with high-quality biospecimens paired with robust clinical data. Safe, immediate specimen availability will accelerate clinical trials with the underpinning of basic science research. Progress made on the discovery of potential biomarkers involved in disease advances and MCM development can be fast-tracked by trained, expert teams dedicated to obtaining, maintaining, and distributing high-quality specimens with harmonized collection and handling techniques. A distributed biorepository model with a centralized data repository and shared governance structure would facilitate rapid clinical research response while also allowing for broad access to specimens at various biosafety levels.

This model is currently in use by NETEC SPRN and SARI-PREP. This allows sites participating in clinical research to maintain subsets of their collected specimens while contributing to broader biobanking efforts and supports downstream basic and translational research initiatives as well as potential surveillance efforts. The network must be able to collect specimens and data that are not associated with existing research studies to inform baseline health questions, support preexposure elements of longitudinal research, advance the preclinical agenda for many MCMs, and provide control material for translational research questions associated with emergency clinical trials. Given the value of these specimens outside of a specific emergency, it is critical to build a specimen bank independent of specific clinical trials and research studies that can be accessed and relied upon for novel inquiry via secondary use protocols.

c. Identifying and incentivizing research institutions and networks and building diversity and equity

Building research infrastructure to ensure that clinical trials of interventions during PHEs are conducted with the principles of diversity and equity is critical to ensuring that they meet the needs of the impacted populations quickly. We recommend the following steps for building diversity and equity in emergency clinical trials:

1. Establish clear policies and guidelines. Develop and implement policies that ensure diversity and equity in the recruitment, selection, and retention of study participants that are adaptable to the needs of individual locations but consistently applied across all participating sites.

2. Review individual site approaches to local context review (eg, state and local laws, conflict-of-interest policies, standard institutional language for consent, and local safeguards for vulnerable populations) when using a single or central IRB to ensure that the specific needs of individual communities are being met and existing health inequities are not being ignored or exacerbated to negatively impact the diversity or access of the study populations.

3. Engage with diverse communities. Work with community organizations and leaders to identify and address barriers to participation in research and to inform communities about the goals and objectives of the research.

4. Increase representation of diverse populations in research studies. Ensure that clinical trials and other research studies are designed to be inclusive and representative of the populations they are intended to benefit and engage research partners that serve diverse communities.

5. Promote diversity and equity in the research workforce. Encourage the recruitment and retention of a diverse research workforce, including researchers from traditionally underrepresented groups through specific incentives for minority researchers and established mentorship programs.

6. Collect and analyze data on diversity and equity regularly throughout the conduct of research. Monitor and track the diversity of participants in both warm-base research (see Section c below) and emergency clinical trials and use these data to identify and address any disparities in participation.

7. Widely disseminate research findings. Share research findings with diverse communities and stakeholders in a timely manner to ensure that the benefits of research are widely distributed.

8. Use digital health technologies (DHTs) for improved access to clinical research. Various DHTs would improve both awareness of and access to trials for many less-accessible populations (eg, those who are rural, homebound, or lacking access to academic medical institutions). They may also improve the fidelity of longitudinal and follow-up data through the use of wearable sensors, data collection and reporting apps, and telemedicine.

9. Partner with healthcare sites that are not traditionally included in clinical trials research such as critical access hospitals, federally qualified health centers (FQHCs), and retail healthcare sites (eg, pharmacies and urgent care centers.) These sites can be engaged in clinical research through warm-base studies to provide exposure to fundamental research activities, partner with academic medical institutions in their region to develop research skills, and formalize the necessary regulatory frameworks. FQHCs may also be able to support both the socialization of research initiatives and the dissemination of research findings back to the community.

d. Warm-Base Research

The strategy of each of these networks, both collectively and independently is to build partnerships through the maintenance of a “warm base” to ensure rapid collaborative response in an emergency. A warm base of ongoing clinical research—in the form of prospective observational and interventional studies—is crucial to establish and maintain outside of episodic, fragmented initiatives during PHEs. Having this research infrastructure in place allows clinical sites to rapidly pivot and implement clinical trials against a novel emerging disease.

The RIN takes a stepwise, iterative approach to warm-base research engagement by scaling up the requests (and ultimately, the capabilities) of participating sites, including responding to weekly health system stress queries that assess the supply/demand balance of patient care resources, including MCMs; participation in a

single IRB; enrolling patients into observational protocols; and participation in multicenter platform clinical trials with multisite data sharing.

SPRN initiates warm-base research by engaging in observational research initiatives with healthcare worker vaccinees. A multisite observational protocol with biospecimen collection and a common data element dataset engages all SPRN sites in the participation of observational research, which has the added benefit of building a longitudinal cohort of high-risk individuals with biospecimens and associated rich clinical metadata. This mechanism also provides a regulatory "lab" for testing the flexibility of the regulatory frameworks that govern multisite clinical research across the network and ensures strong relationships between all sites' investigators, regulators, legal teams, and clinical coordinators.

SARI-PREP builds and maintains observational clinical protocols that broadly address severe respiratory illness, building an infrastructure that lays the groundwork for improving clinical care through a better understanding of emerging and seasonal respiratory diseases and their treatments. The SARI-PREP model sustains a collaborative research model that links critical care researchers across the country and can be used to identify early warning signals and lead clinical research teams into a collaborative emergency research response.

Observational warm-base research contributes to the evidence base for clinical medicine, builds research resources such as harmonized biobanks and longitudinal data sets, and facilitates emergency research by building; routinely testing; flexing the regulatory, ethical, and legal frameworks; and maintaining the community relationships needed to conduct multisite emergency clinical trials.

An additional warm-base element that provides substantive value and enhanced capability to the network is the conduct of drills and exercises. This allows for engagement with new (and unlikely) partners and strengthens existing partnerships in a controlled environment.

e. Emergency Master Agreements (EMAs)

In emergency clinical trials, the work will always be contextual to that emergency so, while an EMA does not solve the need for event-specific contracting, it may expedite the contracting and regulatory requirements. EMAs establish expectations and existing relationship between institutions, which allows for a bit more nimbleness and flexibility in an emergency.

Additionally, elements of an EMA may be used to facilitate research initiation timelines. The SPRN, RIN, and SARI-PREP leverage the National Center for Advancing Translational Sciences' (NCATS) Streamlined, Multisite, Accelerated Resources for Trials (SMART) IRB to execute reliance agreements across the respective networks, which allows for rapid use of a single IRB (sIRB) in an emergency. The SPRN IRB (through the University of Nebraska Medical Center) has a rapid response IRB mechanism that further expedites the IRB processes. Local context is an essential element of the single IRB process and, in addition to informing the local IRB application, it can be used to inform the necessary flexibility that must be built into an EMA template. This flexibility is critical to broad adaptation and use of an EMA. Further, the networks can leverage existing contract mechanisms to facilitate data sharing and material transfer through templated contract language.

The network-of-network concept could also be leveraged to develop a key stakeholder group that can be convened to inform the critical functional elements of an EMA that would not only meet the needs of

sponsors and regulators but also be acceptable to research sites with highly variable degrees of experience with research agreements. Below are some essential elements of a successful EMA.

Essential Elements of an Emergency Master Agreement	
Pre-positioning	An executed EMA (negotiated prior to an emergency) can expedite the process of starting a clinical trial in an emergency situation by preestablishing priority terms and conditions and by establishing clear terms and conditions for the conduct of the trial.
Flexibility	Flexibility must be built in to the structure of the EMA to allow for changes to be made to the protocol or for the use of alternative or complementary treatments or procedures if necessary.
Scalability	The EMA must allow for scalable and adaptive trial designs that flex based on a changing outbreak landscape as well as updates to the trial design.
Event-specific addenda	Pre-positioning carries a risk of having an agreement with parameters that may negatively impact the trial's success. The EMA must allow for site- or event-specific addenda that facilitate trial success.
Local context review	Local context can have a significant impact on the conduct of a clinical trial and its results, so EMAs must facilitate local context review to ensure that a clinical trial considers the specific needs and realities of the communities in which it is being conducted. This can help increase the acceptability and feasibility of the trial, improve its chances of success, and improve both its equity and diversity elements.

References:

1. Lurie N, Manolio T, Patterson AP, Collins F, Frieden T. Research as a part of public health emergency response. *N Engl J Med*. 2013 Mar 28;368(13):1251-1255. doi: 10.1056/NEJMsb1209510.
2. Postelnicu R, Srivastava A, Bhatraju PK, et al. Severe Respiratory Infection-Preparedness: protocol for a multicenter prospective cohort study of viral respiratory infections. *Crit Care Explor*. 2022 Oct 20;4(10):e0773. doi: 10.1097/CCE.0000000000000773.
3. Lowe AE, Kraft C, Kortepeter MG, et al. Developing a rapid response single IRB model for conducting research during a public health emergency. *Health Secur*. 2022 Jun;20(S1):S60-S70. doi: 10.1089/hs.2021.0181.
4. Randolph AG, Bembea MM, Cheifetz IM, et al; Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network. Pediatric Acute Lung Injury and Sepsis Investigators (PALISI): evolution of an investigator-initiated research network. *Pediatr Crit Care Med*. 2022 Dec 1;23(12):1056-1066. doi: 10.1097/PCC.0000000000003100.
5. Cobb JP. Clinical investigation during public health emergencies: the Resilience Intelligence Network. *Am J Public Health*. 2019 Sep;109(S4):S268-S270. doi: 10.2105/AJPH.2019.305215.
6. Measer GT, Maher CT, Hu-Primmer J. Monitoring and assessment of medical countermeasures as part of a public health emergency response. *Am J Public Health*. 2018 Sep;108(S3):S226. doi: 10.2105/AJPH.2018.304526.

Consortium for State and Regional Interoperability

January 27, 2023

Submitted electronically via: datacollectionforclinicaltrials@ostp.eop.gov

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RE: Request for Information (RFI) On Clinical Research Infrastructure and Emergency Clinical Trials

Dear Ms. Sipes,

The Consortium for State and Regional Interoperability (CSRI) sincerely appreciates the opportunity to provide information on ways to build U.S. capacity to carry out emergency clinical trials and strengthen the overall U.S. clinical trial infrastructure, including potential governance models. The capacity to carry out coordinated, large-scale clinical research has been shown to be of vital importance during an outbreak of infectious disease or other public health emergency. Additionally, the need to understand the safety and efficacy of therapies within underserved populations as a way of reducing disparities and advancing equity is a moral and scientific necessity. We are eager to work alongside you to achieve our mutual goal of enhancing public health system capabilities and emergency clinical trials infrastructure to ensure and expediate the development of actionable information to address future outbreaks and emergencies in a timely, well-informed, and equitable way.

Overview: CSRI & Health Data Utilities

CSRI represents a collection of six of the nation's largest and most innovative nonprofit health data networks serving Arizona, California, Colorado, the District of Columbia, Iowa, Indiana, Maryland, West Virginia, and Nebraska. The founding members of CSRI are leading health information exchanges (HIEs) that manage the exchange of health information for over 80 million individuals, enable information exchange for more than 370 hospital facilities and thousands of healthcare providers, and are experts in data governance, privacy protection, and identity management. We believe that clinical health information sharing networks should be a crucial part of the "warm base" that the Office of Science and Technology Policy (OSTP) is seeking to strengthen and maintain.

By serving as neutral and widely trusted hubs of information, HIEs have become integral parts of the health care system. HIEs process millions of health care transactions daily and facilitate the coordination of care among an individual's multiple care providers and payors by providing the capability to electronically move health information among disparate systems. Among many other benefits, HIEs have been shown to improve the quality and safety of patient care by reducing medication and medical errors, eliminating redundant or unnecessary testing, improving public health reporting and monitoring, and reducing health related costs.

CSRI member organizations have demonstrated not only the aforementioned capabilities but have also evolved beyond these capabilities to serve as reliable data repositories that enable secure access to high-quality health data for all credentialed utility stakeholders, including states, payors, providers, vendors, and academics. CSRI member organizations have the ability to provide data-driven support to government programs and strategic priorities and solve some of the most pressing challenges associated with making

clean, matched, and normalized clinical data available for research, quality improvement, and programs to improve public and population health.

Given these expanded functions, CSRI member organizations all serve as **health data utilities (HDUs)** for our respective states. While some variation exists, we serve health care providers, payors, Medicaid agencies, and public health departments. HDUs bring together health data from disparate sources including ambulatory providers, laboratories, post-acute providers hospitals, health plans and public health. The utility cleans, matches, and attributes this data, making it available to a wide range of health care stakeholders in a given geography through standardized tools, data services and reports. Depending on a state's needs, the HDU may also serve as (or include data from) social service referral platforms, prescription drug monitoring programs, and all payer claims databases. Neutral, trusted, nonprofit HDUs serving as a public-private partnership can securely bridge and connect historic data silos to rapidly provide data and data insights to meet individual, public, and population health use cases directly aligned with the needs of OSTP.

Background: CSRI Emergency Response & Research Capabilities

Given our significant health data management capabilities, CSRI is well-suited to collect large data feeds for research purposes in a timely and secure manner. Our existing foundation of provider relationships, proven efficiency, and capacity for expansion by seamlessly linking HIEs across states offer a unique opportunity to benefit from federal infrastructure investments, while scaling quickly to meet the public health demand for novel public health emergencies. As noted in a recent blog from the HHS Office of the National Coordinator for Health IT (ONC),

> *[S]tate and local HIEs, which in aggregate receive EHR data from more than 60 percent of U.S. hospitals, could be better used as a source of patient-level electronic health data for large-scale research. HIEs routinely collect patient data from a variety of sources and then facilitate the exchange of patient health information with clinicians, public health agencies, and laboratories. Increased use of this data for patient-centered research could help facilitate research activities, including in public health emergencies such as COVID-19.*

The COVID-19 pandemic response required rapid and real-time access to transmission and vaccination data as well as bed and medical equipment availability, viewable by demographic trends, comorbidities, geography, and other key characteristics. In CSRI member states, mature HIEs served as critical aggregators and repositories for such information, enabling their states to engage in strategic, coordinated, and efficient pandemic surveillance and response efforts supported by real-time data. These networks rapidly deployed solutions including: sharing data on the spread of the virus for frontline healthcare workers; enabling public health departments to quickly gain valuable insights on trends for testing and vaccination; and, providing real-time hospital case rate and resource utilization data. Such public-private partnerships between states and HDUs not only improved the public health response but also served as important data resources for clinical systems working to treat and monitor patients.

Additionally, these clinical networks were often able to enrich data held in immunization systems by providing important contextual data – such as race, ethnicity and contact information– that have high relevance for both public health experts and policymakers. In several of our member states, state governments and public health departments have relied on CSRI data networks to populate race and ethnicity data needed for COVID-19 public health emergency priorities, such as testing and vaccination

outreach, to understand the spread and response of the pandemic among different geographic and demographic populations.

While some states can leverage these existing systems, the lack of processes in place for developing emergency clinical trial protocols and for capturing trial data through consistent data elements reported across participating sites has significantly hampered U.S. capability to conduct clinical research in the face of a health-related emergency.

We believe there is an important opportunity to leverage the significant health information network infrastructure that already exists in many states to enhance and strengthen the U.S emergency clinical trials effort.

We are pleased to offer our responses to the following questions in support of this opportunity and we would appreciate the opportunity to meet and discuss these areas in additional detail.

Specific Responses

1. *Governance for Emergency Clinical Trials Response.*

The members of CSRI would stress the importance of nonprofit, state-level health data networks with existing patient and provider-level connectivity in any governance structure. The challenge of collecting data on a national level was demonstrated during COVID-19 as health providers and federal agencies alike had challenges collecting and aggregating data in real time. Efforts to rapidly scale new capabilities struggled, while many parts of the existing health care infrastructure, like HIEs, were able to stretch to meet new demands. Specifically, many HDUs have existing data aggregation, data quality, and data governance procedures supported by state and federal legislation and deployed to consumers, participants, and government agencies in near real-time. The foundational infrastructure in data sharing agreements and technology ensure a nimble response to most situations.

State-level clinical health data networks rose to the challenge of the COVID-19 pandemic, maintaining real-time detailed covid tracking databases, building vaccine reporting interfaces, and helping many small providers automate data entry to meet new reporting demands. These networks are a perfect way to maintain the “warm base” capabilities for clinical health information sharing that will be needed in a time of crisis. These networks have up-to-date networks of health providers, tried and tested technologies that have exchanged millions of patient records, and strong local and regional contacts and relationships to mitigate challenges that do arise. Many already regularly engage in support for health data research, including work on clinical trials.

In addition, local HIEs are experts in the privacy laws of their states and the concerns of their citizens, enabling the federal government to more efficiently navigate this patchwork of systems while still maintaining patient privacy and trust. Our HIEs have robust governance structures already in place including comprehensive board oversight, internal data governance, robust interoperability and quality programs, and relationships with healthcare collaboratives. These existing structures can be scaled quickly and effectively while utilizing existing relationships to maximize data sharing and trust among the health data ecosystem.

Given our health data expertise and experience addressing not only COVID-19 but also longstanding chronic disease and public health challenges, CSRI strongly requests to be included in any conversations around the development of this new national capacity and its governance. We believe it is also critical to

engage HIEs at the outset of this planning process to solve for any required advanced consent or other governance measures before any emergency actions are needed to ensure the speediest exchange of data from the HIE when needed.

2. *Identifying and Incentivizing Research Institutions and Networks; Building Diversity and Equity.*

As noted, state clinical health data networks maintain relationships with the majority of health providers in their states neutral to providers or health systems and location agnostic, meaning they are well suited to support a wide network of organizations participating in research. To understand the impacts of clinical trials, you need the widest and most diverse net of providers possible to successfully understand how small rural providers and large urban hospitals would differ in implementing the same treatments. HIEs already have these existing relationships and partnerships and thereby can assist in the outreach and recruitment of facilities for emergency clinical research studies. This state-wide presence can also bolster public awareness by leveraging the existing communication channels to help recognize and communicate any facility's commitment to the public.

Mature HIEs contain the most robust and applicable data to support accurate and rapid identification of target populations who may be needed for a clinical trial. In addition to demographic information, prior health histories, and health risk factors, many other factors could be captured from a clinical health information record leading to stronger and faster targeting and subsequent data analysis than would be captured through a siloed clinical trial effort.

3. *"Warm Base" Research.*

HDUs are perfectly positioned to support a "warm base" model of collaboration. The health data networks remain a constant and near real-time source of comprehensive health data with our CSRI members continuing to innovate to improve longitudinal health records even including social care data in some states. This existing data can continuously support "warm base" research efforts while maintaining local governance and trust. HDUs are uniquely situated to assist in identifying target infections and understanding important population differences by differentiating variables such as race, gender, or geographic location. CSRI members already support continuous research models through healthcare collaborations and academic partnerships. The involvement in a "warm base" research model to provide the most comprehensive health data for clinical research would be a direct and vital application of these robust health data networks which are a result of more than a decade of dedicated state, federal and industry investment.

5. *Identifying Viable Technical Strategies for Data Capture; Gathering Information About a Potential Data Capture Pilot*.

We look forward to this information request, and believe that fully interoperable, nonprofit state health data networks are well positioned to support the data capture needs of an emergency clinical trial infrastructure.

Conclusion

Thank you for your leadership in examining this pressing and important issue. We look forward to partnering with you to advance the national interest and strengthen our health research capabilities.

Please feel free to contact me with any questions about the capabilities of state health data networks at morgan.honea@contexture.org or (720) 285-3230.

Cordially,

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Subject: Emergency Clinical Trials RFI

Dear Dr. Grail Sipes,

Thank you for the opportunity to respond to the RFI: *Strengthening Capacity for Emergency Clinical Trials*. I write on behalf of the Federation of Associations in Behavioral and Brain Sciences (FABBS), a coalition of 29 scientific societies and 60 academic departments that come together to equitably advance the rigor, impact, and accessibility of our disciplines. We are grateful to see this OSTP effort.

Broadly, and specific to the RFI, FABBS would like to underscore the critical role of the behavioral sciences to mitigate and address the COVID-19 pandemic. Our members contribute a wide range of expertise critical to pandemic preparedness that were regrettably overlooked and underutilized in the U.S. response to COVID-19. This administration could learn from this enormously consequential mistake by investing in behavioral science to prepare for the next pandemic. FABBS scientists address critical questions at the core of understanding vaccine uptake and resistance, including science communication, threat and risk perception, social norms, stress and coping, leadership styles, individual vs. collective interests, decision making and cognitive processing. Collectively, our expertise comes together to answer fundamental questions about how and why people, organizations, and groups behave in the way they do within wider societal and economic contexts.

In the early days of the pandemic, policymakers relied completely on behavioral interventions to reduce the spread of the virus – mask wearing, hand washing, and physical distancing. Even after effective vaccines were widely available, human behavior continued to play a large role due to many people being hesitant to get vaccinated. Former NIH Director Dr. Francis Collins has said that, according to a Kaiser Family Foundation study, as of December 2022, roughly 330,000 people had died in the United States because they had chosen to forgo the vaccine.(https://www.washingtonpost.com/washington-post-live/2022/12/07/transcript-trust-science/) While many of these behavioral interventions are extremely low risk, some are classified as clinical trials, triggering all of the cumbersome reporting requirements, needlessly delaying effective implementation.

These comments reflect input from FABBS scientists and the challenges that they faced and opportunities for streamlining clinical trials processes to accelerate implementation of effective interventions.

1. **Governance for Emergency Clinical Trials Response**. While an invaluable tool, behavioral interventions often have far fewer risks than biological ones – and should be treated accordingly. FABBS recommends

aligning complexity of clinical trials approval with the level of risk to health. The current NIH definition of clinical trials, which includes behavioral interventions, can needlessly delay approval for extremely effective and very low risk behavioral research. FABBS recommends revisiting the NIH definition of clinical trials. Given that behavioral interventions are currently considered to be clinical trials, these interventions should be explicitly included in efforts to facilitate emergency approval. Specifically, our scientists have lamented the heavy burden of complying with the additional review of the NIH Data Safety Monitoring Board as one example.

2. **Identifying and Incentivizing Research Institutions and Networks: Building Diversity and Equity**. Clinical trials compliance requires considerable time and specific knowledge and is, reportedly, a significant burden to researchers and health care professionals who are not affiliated with well-resourced infrastructure. FABBS encourages OSTP to consider the unintended barriers of clinical trials compliance to diverse and underserved communities and networks. Furthermore, engaging diverse institutions and networks through more affordable and manageable interventions, has the potential to lay the groundwork for growing the capacity.

   By way of illustration, the Behavior Change for Good Initiative (BCFG at the University of Pennsylvania (https://bcfg.wharton.upenn.edu/vaccination/) partnered with two regional health systems to test messaging techniques, ultimately increasing vaccination rates by as much as 11 percent. This critical work was supported by two NIH Roybal Centers. BCFG has dedicated research staff who made it possible, with support from the Roybal Centers, to navigate the complexity of clinical trial compliance in a short timeframe. It would have been far more difficult for an individual research team to accomplish this without this level of infrastructure. Even with this team of professionals in place managing BCFG's project, there were delays to the intended launch date because the NIH was unable to convene a necessary DSMB in a timely manner.

3. **"Warm Base" Research.** While waiting for the FDA approval of the COVID vaccine, BCFG scientists anticipated the potential challenges around vaccine uptake and worked to identify effective practices for increasing vaccination rates. In addition to their study with health systems, BCFG partnered with Walmart pharmacies to test 22 text reminders of differently worded and timed text reminders to patients to nudge flu

vaccination. The experiment demonstrated the effectiveness of behaviorally-informed reminder messages for increasing vaccination rates and the benefits of testing such reminders at scale to identify the key features that added value. The results are captured in this important article: A 680,000-person megastudy of nudges to encourage vaccination in pharmacies (https://www.pnas.org/doi/10.1073/pnas.2115126119).

FABBS also encourages OSTP to recognize the devastating mental health consequences of the pandemic as our country works to prepare for future pandemics. Thanks to previous research, largely funded by the National Science Foundation (NSF), researchers have identified characteristics of communities at the greatest risk of disproportionate negative consequences. Accordingly, researchers have the opportunity to work in at-risk communities in advance of future outbreaks or crises to both establish a baseline understanding and develop 'warm bases'. NSF has continued to lay the groundwork for warm bases. In Fall 2021, in partnership with foundations, Social Science Research Council (SSRC) launched the Mercury Project, mobilizing social and behavioral scientists in a search for cost-effective and scalable solutions to build vaccination demand and healthier information environments. https://www.ssrc.org/programs/the-mercury-project/call-for-proposals/

Looking at the experience of FABBS scientists, the National Institutes of Health (NIH) has not prioritized this sort of research.

As the pandemic played out and FABBS researchers turned to federal agencies to support investigations of pressing questions from the behavioral sciences, our members reported very different experiences at NSF and NIH. NSF was quick and nimble, awarding RAPID grants to investigators across disciplines. This meant that researchers with the potential to help answer key questions were able to turn to NSF for new funding. NIH, on the other hand, was initially limited to providing additional funding only to active investigators. As a result, relevant experts with warm bases, unless currently receiving NIH funds for a separate purpose, were unable to receive support, even if they had the warm base and expertise to conduct critical research during the rapidly evolving COVID-19 pandemic.

4. **Emergency Master Agreement.** The COVID-19 pandemic shined a bright light on the need to invest in the behavioral sciences and develop pathways for incorporating these sciences into practice and policy.

FABBS recommends preemptively developing interdisciplinary research teams with clear and streamlined approval processes. UK Research and Innovation (UKRI) offers a useful example, developing a leadership team to create a 'hub' that will connect stakeholders and drive interdisciplinary innovation in behavioral research to mobilize research into policy and practice. Without existing teams with established practices for clinical trial approval, researchers risk losing precious time navigating clinical trial processes developed with purely biological models in mind.

In summary, FABBS urges OSTP to explicitly include consideration of the behavioral sciences in all efforts to prepare for future pandemics. In their 2021 update to their strategic plan, the NIH clarified their mission to explicitly include behavioral ---- in addition to biomedical --- research. We recommend that OSTP recognize and reflect this evolution.

Thank you,

Juliane Baron

Executive Director

ACT@POC™
Coalition for Advancing Clinical Trials at the Point of Care

OSTP Request for Information: Clinical Research Infrastructure and Emergency Clinical Trials

Reference: Federal Register Notice: Document Citation: 87 FR 64821, Document Number: 2022-23110

Intro

As member organizations in the Coalition for Advancing Clinical Trials at the Point of Care (ACT@POC™ or "Coalition"), we are pleased to contribute a response to the Office of Science and Technology Policy's recent Request for Information on Clinical Research Infrastructure and Emergency Clinical Trials. The Coalition's aim is to drive the implementation of large-scale clinical trials at the community level—in the doctor's offices and care facilities where most of the U.S. population receives care. Led by a core of health systems, the Coalition is building on the foundational efforts of the VA, PCORNet, and other trial networks to generate regulatory grade clinical evidence at the point-of-care from a broader range of clinical sites. The impact of these collective efforts is to improve patient and provider engagement at sites that do not typically participate in existing clinical research or trial networks.

The Coalition adheres to the following principles:

1. **Engagement of practicing clinicians** in a broader range of care settings to obtain much greater clinical trial participation so research will reflect large and diverse patient populations who are not typically able to participate in clinical research
2. **Development and adoption of tools** that enable straightforward data collection from electronic data systems used to support and improve routine clinical care, to limit the burdens and maximize the benefits for community healthcare providers, who must carve out time during the provision of care to collect data
3. **Collaboration with clinical trial design leaders**, regulators, funders, sponsors, and other stakeholders to assure that clinical trial design features are fit-for-purpose – with relatively simpler design and data collection requirements for products where mechanisms and safety issues are better understood
4. **Enrollment of diverse trial participants** through broader participation in effective community trials. The ack of representation in clinical trials continues to magnify health disparities. Without sufficient representation, optimal prevention, diagnosis, and treatment decisions cannot be made
5. **Reaching a critical mass of participation** in existing and emerging platform trials in areas of unmet need (i.e. registry-based trials that assess multiple therapeutics simultaneously) to enable meaningful, large-scale trials that maximize learning from patient participation and minimize burden on participating hospitals, clinicians, and patients while collecting adequately reliable data
6. **Expectation to improve technology supports and capabilities** to conduct frontline studies in community settings over time, enabling increasingly streamlined trial participation and supporting care improvement.

With these principles in mind, our response to the RFI is focused on the following topics:

- "Warm base" research
- Value of point-of-care approach for "warm base" research
- Identifying and incentivizing research institutions and networks to build diversity and equity

"Warm Base" Research

In terms of initial steps towards broadening participation in clinical trials, the Coalition views building a national "warm base" research network as a top priority. "Warm base", as defined by the Office of Science and Technology Policy, refers to studies that not only gather data under a particular clinical research protocol, but also serve the function of keeping trial sites in a state of readiness to undertake additional or future research. A baseline "warm base" research network would be an ecosystem that can attract patients to participate in clinical trials attempting to address their greatest health needs. Leveraging the already-existing capacity built within a "warm base" research network will - greatly improve the capability of communities across the United States to respond in an emergent clinical research challenge.

Disease areas for trial protocols

The United States can construct a nimble "warm base" research network that responds to infectious, chronic, and rare diseases that place a heavy burden on patients and their families. Such a network would enable improved access for communities that have been underserved by health care and clinical trial networks and target chronic diseases, including cardiovascular diseases, diabetes, and asthma. A country-wide "warm base" research network will be most sustainable if designed also to generate evidence on interventions for diseases that exhibit the highest burden on health care systems.

Regarding the extent to which "warm base" research may target infectious disease versus other chronic or rare diseases, value exists in building a network that can enroll a diverse population representative of the disease in question. Any trial initiated within this "warm base" network needs to be large enough to generate actionable evidence that ultimately benefits those who enrolled in the study. Community-based sites of care can partner with larger academic medical centers to both address chronic and rare disease trial opportunities, enroll representative patient populations, and establish pre-emptive working relationships ahead of the need for infectious disease trials. For example, during the COVID-19 pandemic, several large academic medical centers have leveraged existing community partnerships to better understand the safety and effectiveness of treatments, like monoclonal antibodies in an outpatient setting.

The Coalition for Advancing Clinical Trials at the Point of Care is identifying best practices to engage and activate more sites in clinical research at the point-of-care. ACT@POC values collaborating with a variety of stakeholders to broaden clinical trial participation, enrolling a diverse group of participants, and designing trials that address unmet medical needs. Activation of more sites in creation of a "warm base" research network will facilitate the implementation of values of our Coalition.

Training implementation and mechanisms for clinical research staff

Despite levels of burnout that preexist the COVID-19 pandemic, providers are more than willing to engage in clinical research, especially work that results leads to improved patient outcomes. The

Coalition is currently strategizing on ways health systems can facilitate a culture of provider and staff participation in research, including promoting protected research time and allowing providers and staff to investigate questions of mutual interest with other stakeholders.

In general, clinical research staff stand to benefit most from training approaches that are broad-based with transferrable skills and lessons that apply to a variety of trial designs. For sites with staff inexperienced with clinical research, mechanisms that provide iterative and supportive feedback can empower knowledge and best-practice sharing. Principles from the NIH-sponsored Radx initiative also can facilitate clinical research staff training, including culturally and linguistically responsive messaging as well as alterative payment models that enable systems to cover training for all needed research staff.

A holistic training approach would be furthered if part of an expanded health system capacity for emergency responses that incorporates training for clinical research. The U.S. Center for Medicare & Medicaid Services (CMS) could modify existing hospital emergency preparedness Conditions of Participation to include dedicated requirements for clinical research capabilities.

To conduct clinical research, sites must have the tools, technology, and expertise to collect, exchange, and analyze research data. Inexperienced sites need accessible, affordable, easy-to-use tools to support data collection and data exchange, as well as training and support for the use of these tools. Digital tools present an avenue for implementing clinical research staff training and support. The Coalition is exploring the use of data and technology "readiness assessments" to validate sites that are able to collect and exchange data reliably prior to their participation in clinical research.

Structure of "warm base" research

A "warm base" research network ultimately will need to be integrated by multiple health care system stakeholders into their workflows to achieve sustainability. This integration will require involvement by both public and private sector stakeholders. A long-term plan for a "warm base" research network will need to include steps to incorporate these public-private partnerships.

A demonstration project supported by funding from one or more federal agencies may help advance engagement in a "warm base" research network. In anticipation of emerging infectious diseases, demonstration projects could serve as pressure testing exercises for the viability and functionality of "warm base" research networks. For publicly supported infrastructure and resources, transparency and clear expectations-setting can help private stakeholders understand the need and timeline for investment. By providing good publicly funded examples, federal agencies can ensure that the private sector has a roadmap to follow for further development.

Any "warm base" research network will need to be capable of generating regulatory-grade evidence. As we saw in the COVID-19 pandemic, many trials were planned and conducted that did not contribute to our ability to make critical, time-sensitive decisions.[1] To best use limited resources "warm base" capacity should be capable of robustly informing decision-making by government and public health agencies in an emergency setting.

A Point of Care Approach to Maximize "Warm base" Research

Given the considerations above, we believe any "warm base" research capacity building should leverage point-of-care approaches. Point-of-care approaches to clinical trial conduct are approaches that

integrate research and care delivery and typically feature designs components such as simplified data collection, completion of research activities in usual care conditions, and integration of research and care delivery workflows. Such approaches have the potential to increase the ability for a nimble, responsive clinical trial network able to capture the data needed due to its simplified protocols without unnecessary complexity. This approach is particularly well-positioned to accelerate research for existing therapies that could be repurposed for health emergencies, such as dexamethasone and others that were studied during COVID. Leadership at the U.S. Food and Drug Administration have highlighted this potential as well[1–4].

Integrating clinical research into clinical practice through well implemented point-of-care approaches can provide many benefits for "warm base" research capacity. For example, a point-of-care trial approach would leverage data typically collected in electronic health records during routine clinical practice, leading to simplified data collection. This simplified data collection reduces the entry barriers to research participation, enabling broader reach into more settings, including community settings and providers that may not traditionally participate in clinical research. The focus on well-understood, repurposed therapies also provides an opportunity to streamline data collection on adverse events. Additionally, these approaches encourage broad, streamlined eligibility criteria and a focus on objective endpoints that are collected in routine practice and are more straightforward to adjudicate than some traditional trial endpoints (e.g., hospitalization or mortality). Such approaches also aim to include randomization, a crucial component for generating robust evidence. Designing the nation's "warm base" capacity, with point-of-care trial approaches in mind, will ensure that the capacity is streamlined, ready to respond to health emergencies, and has a broader reach than many of our traditional systems.

The vision outlined above is a goal our Coalition and others are reaching for. Most of our national health care infrastructure is not yet ready to implement all of the necessary steps to achieve this goal. Data systems are fragmented, provider incentives are misaligned, and there are questions about whether regulators and payers will accept evidence from point-of-care trials. Additional thinking also is needed on how best to leverage Institutional Review Boards and ensure patients are appropriately consented to trials.

Despite these challenges, there are numerous examples of settings and therapeutic areas exist where providers have successfully employed point-of-care trial and point-of-care style approaches. The U.S. Department of Veterans Affairs Health System conducted point-of-care trials testing interventions for improving treatment of diabetes, cardiovascular disease, and COVID-19. The National Patient-Centered Clinical Research Network implemented a point-of-care style approach, ADAPTABLE, for investigating use of different aspirin doses in the treatment of atherosclerotic cardiovascular disease. The United Kingdom (UK) leveraged their National Health Service hospital system to coordinate a point-of-care style platform trial, RECOVERY, which assessed multiple interventions for treatment of COVID-19. Additionally, general practitioner practices in the UK evaluated interventions for cardiovascular and chronic obstructive pulmonary diseases in the Retropro and eLung trials, both of which used point-of-care approaches.[4–6] Building out "warm base" research capacity is a strategic opportunity to further integrate clinical research into clinical practice and build a robust research infrastructure at the point-of-care that will not only serve the United States but also the world in health emergencies and in confronting other burdensome diseases.

Identifying and Incentivizing Research Institutions and Networks to Build Diversity and Equity

Effective ways to increase diversity and expand clinical research

Point-of-care trials may increase the diversity of clinical trial enrollment, as community care settings typically more closely reflect the demographics of their populations than trials at academic medical centers. In addition to simply placing trial sites in community settings, community outreach may be beneficial as participants may be more likely to enroll and trust the results of clinical trials when trialists work with community leaders to implement and share the results of trials with the community.

The point-of-care approach also may decrease burdens on participants, allowing for broader participation in clinical trials. Many traditional trials present accessibility concerns for patients, including those related to logistics, finances, and awareness of clinical trials, in general. Point-of-care trials may be more accessible, as patients typically have fewer logistical barriers. For example, point-of-care trials do not feature research-only visits to care sites and patients may have to travel shorter distances to their community site as opposed to often-distant academic medical centers.

Fewer transportation and time burdens allow point-of-care trials to enroll more patients of various backgrounds and may alleviate some of patients' financial constraints related to trial participation. However, trials may need to use alternative payment models that cover the cost of trial participation so that uninsured or underinsured patients may participate.

In many cases, patients may not be aware that they are eligible to participate in clinical trials. Point-of-care trials can reverse this lack of awareness and result in increased patient awareness of clinical trials, and ultimately increase trial representativeness. In the point-of-care approach, a patient would be screened for eligibility, educated, enrolled, and consented in their typical setting, allowing them to easily participate in a trial for which they are eligible. Patients also may trust their typical care team more than clinicians at distant or new sites, which may encourage more patients to enroll that have been typically excluded from clinical research.[7]

Other features of the point-of-care approach may encourage trial representativeness. For example, broadened and streamlined eligibility criteria for enrolling patients in point-of-care trials may increase trial diversity as restrictive eligibility criteria has traditionally disproportionally excluded patients from racial and ethnic minorities.

In addition, collecting data on race and ethnicity, as well as self-reported data on sexual orientation and gender identity (SOGI), disability, preferred language, and sociodemographic information can help investigators understand the representativeness of their enrolled patient populations.[8,9] Rather than just considering trial diversity relative to the population at large, investigators should consider what is known about the patient population for the disease or condition being studied, including demographic and non-demographic factors, in order to ensure their trial enrollment is representative relative to real-world populations. These considerations may include barriers to accessing trials that are specific to patients with the disease or condition under investigation. Additional considerations for pregnant and lactating patients may exist as well as for patients with mental or physical disabilities.

Conclusion

The Coalition for Advancing Clinical Trials at the Point of Care recognizes that developing and maintaining an emergency clinical trial network is a collaborative exercise. We desire continued partnership with the Office of Science and Technology Policy and the FDA as well as other Federal agencies and organizations that are leading the building out of critical trial capacity. Our Coalition will continue to ascertain best practices for encouraging provider and patient participation in point-of-care trial research. Additionally, we'll work to encourage the development of effective digital tools and technological supports for data collection and propose policy considerations to overcome barriers for point-of-care clinical trial creation. We believe that robust "warm base" research capacity integrated into routine care using point-of-care approaches will result in more practical evidence generation and ultimately better health outcomes both during and between health emergencies and we look forward to future opportunities to contribute to the design and implementation of such capacity. If you have any questions or would like to follow up, please contact Trevan Locke (trevan.locke@duke.edu) and Brian Anderson (briananderson@mitre.org)

ACT@POC Member Organizations

Ascension

CURE Drug Repurposing Collaboratory

CVS Health

Duke-Margolis Center for Health Policy

Duke University Health System

Emory-Morningside Center for Innovative and Affordable Medicine

Intermountain Health

Medable

Mayo Clinic

MITRE Corporation

The Broad Institute

University of Massachusetts Medicine

University of California Irvine

Vanderbilt University Medical Center

References

1. Bugin K, Woodcock J. Trends in COVID-19 therapeutic clinical trials. *Nat Rev Drug Discov*. 2021;20(4):254-255. doi:10.1038/d41573-021-00037-3

2. Peto L, Horby P, Landray M. Establishing COVID-19 trials at scale and pace: Experience from the RECOVERY trial. *Adv Biol Regul*. 2022;86:100901. doi:10.1016/j.jbior.2022.100901

3. Califf RM, Cavazzoni P, Woodcock J. Benefits of Streamlined Point-of-Care Trial Designs: Lessons Learned From the UK RECOVERY Study. *JAMA Intern Med*. 2022;182(12):1243-1244. doi:10.1001/jamainternmed.2022.4810

4. Propes C, Hendricks-Sturrup R, Sheehan S. Point-of-Care Clinical Trials Intergrating Research Care Delivery.pdf. *Duke-Margolis Cent Health Policy*. Published online May 11, 2022. Accessed June 15,

2022. https://healthpolicy.duke.edu/sites/default/files/2022-05/Point-of-Care%20Clinical%20Trials%20Intergrating%20Research%20Care%20Delivery.pdf

5. Branch-Elliman W, Ferguson R, Doros G, et al. Subcutaneous sarilumab for the treatment of hospitalized patients with moderate to severe COVID19 disease: A pragmatic, embedded randomized clinical trial. *PLOS ONE*. 2022;17(2):e0263591. doi:10.1371/journal.pone.0263591

6. D'Avolio L, Ferguson R, Goryachev S, et al. Implementation of the Department of Veterans Affairs' first point-of-care clinical trial. *J Am Med Inform Assoc JAMIA*. 2012;19(e1):e170-176. doi:10.1136/amiajnl-2011-000623

7. Clark LT, Watkins L, Piña IL, et al. Increasing Diversity in Clinical Trials: Overcoming Critical Barriers. *Curr Probl Cardiol*. 2019;44(5):148-172. doi:10.1016/j.cpcardiol.2018.11.002

8. Xiao H, Vaidya R, Liu F, Chang X, Xia X, Unger JM. Sex, Racial, and Ethnic Representation in COVID-19 Clinical Trials: A Systematic Review and Meta-analysis. *JAMA Intern Med*. Published online December 5, 2022. doi:10.1001/jamainternmed.2022.5600

9. Kahn JM, Gray II DM, Oliveri JM, Washington CM, DeGraffinreid CR, Paskett ED. Strategies to improve diversity, equity, and inclusion in clinical trials. *Cancer*. 2022;128(2):216-221. doi:10.1002/cncr.33905

January 27, 2023
Submitted via electronic mail

To: The Office of Science and Technology Policy
From: Verily Life Sciences, LLC
Re: The Office of Science and Technology Policy's Request for Information (RFI) on Clinical Research Infrastructure and Emergency Clinical Trials (FRN 2022-23110)

Verily thanks the Office of Science and Technology Policy (OSTP) and the National Security Council (NSC) for the opportunity to provide a response to the OSTP's Request for Information (RFI) on Clinical Research Infrastructure and Emergency Clinical Trials.

Verily is an Alphabet company whose purpose is to bring the promise of precision health to everyone, every day. Our work is focused on shifting the paradigm from "one size fits all" medicine to one focused on a more comprehensive view of the individual that leads to a more personalized path forward. We provide solutions across healthcare, from clinical research to care delivery, generating and applying evidence from a wide variety of inputs to change the way people manage their health and the way care is delivered.

In the clinical trials space, Verily has developed software that improves the research experience for participants, sponsors, and study sites alike. Using these tools, we are building disease-specific longitudinal registries that will provide deep insight on participant health and answer questions about which treatments work, and for whom they work best. Today, we work on registries and other clinical studies with organizations such as the American Heart Association, the Crohn's and Colitis Foundation and other leading life science and academic partners.

Verily gained deep experience during the COVID-19 pandemic in building an infrastructure that simultaneously supported patient care, clinical research, and public health response and management. We learned a great deal from this work, especially the need to create practical infrastructure to connect different components of an emergency response–including clinical studies of medical countermeasures, diagnostic testing, clinical care, population health metrics, and public health management.[1] We believe that these types of interconnected components, coupled with an emphasis on participant-centric research, can support an effective clinical research infrastructure for a future public health emergency.

We are pleased to provide comments on components of RFI questions 1 and 2 below.

[1] Arora, J., Mega, J., Abernethy, A., Stadtlander, W. (2022). Connecting Real-World Data to Support Public Health Efforts. Commentary, NEJM Catalyst. https://catalyst.nejm.org/doi/full/10.1056/CAT.22.0040

1. Governance for emergency clinical trials response.

a. Descriptions of models that could be used to establish a U.S.-level governance structure for emergency clinical trials.

Verily supports a federal-level clinical trials structure for large-scale emergency clinical trials, particularly to address the need for geographic diversity in trial enrollment. The governance structure should include participation from a wide range of federal agencies, including those that oversee biomedical research, public health, healthcare payment and delivery, and regulatory review of medical products and intra-agency, state, and local stakeholders when appropriate.

d. Methods for communicating the decision to begin emergency clinical research to institutions and clinical trial networks that can participate in carrying out the research.

It is important to ensure that there is a single, pre-identified decision maker and that clinical research institutions and clinical trial networks know which institution or entity is leading these efforts in advance. Given the significant number of agencies and entities involved in such an effort, the national federal structure or entity described above should serve as the key intermediary between the clinical trial site networks in initiating these large-scale trials, including managing established communication channels. For example, the clinical trial site network, through the federal structure or entity that maintains real-time, two-way communication channels with the research sites, should receive daily (or possibly more frequent) national reports related to the emergency (e.g., hospitalization data, including ICU counts, use of critical medication or medical devices).

i. Criteria for establishing a target number and location of sites needed to support clinical trials in case of emergency.

Clinical trial sites should meet predefined readiness criteria to ensure their capacity to conduct trials in a timely manner and in the setting of a public health emergency. For example, such criteria could include demonstration of capacity to rapidly operationalize a new study protocol and any subsequent study amendments, contact and enroll consenting participants remotely, coordinate trial activities with participants via remote technology where appropriate, and utilize interoperable systems for data capture and sharing.

Sites should have software in place to efficiently manage operational components of a study, including the implementation of a protocol and coordination of study activities. Sites should be able to change these quickly as needed to incorporate protocol amendments. The importance of scalable, flexible, software-based management of

study operations is informed by our experience building and deploying Verily's SignalPath clinical trial management system (CTMS) for a wide variety of research sites.

Trials sites should also have a predetermined plan to recruit and engage with a diverse participant population. For example, sites could develop and maintain a pre-consented research-ready community or build relationships with existing ready communities (e.g., All of Us[2]) or through an integrated care network, including public-sector healthcare networks such as those administered by the Department of Veterans Affairs and Department of Defense. These research-ready communities could pre-consent to a set of initial activities that are designed to facilitate rapid evidence generation and research in an emergency situation.

Trial sites should also be geographically representative of the region(s) of the U.S. affected by the public health emergency. To the extent that the studies are evaluating interventions that are performed or administered in a healthcare setting, the sites for the study should be appropriately representative of relevant contexts of care.

f. Procedures whereby the U.S. Government, together with external stakeholders, could oversee the development of clinical trial protocols and, where appropriate, the selection of investigational agents. It would be particularly helpful to get input on whether there is a role for public-private partnerships in this context.

The importance of input from regulatory reviewers and public health decision makers: We describe several considerations below, but a general theme that deserves emphasis is the importance of early, substantive input from regulatory reviewers at the U.S. Food and Drug Administration (FDA) (and international regulatory bodies, as appropriate) and public health decision makers (e.g., from the Centers for Disease Control [CDC]). This input will ensure that scarce data and research resources are targeted in a way that will inform regulatory and operational decisions (e.g., authorization of a countermeasure for emergency use). The design and implementation of a study should be tailored to study objectives that are confirmed to have value to public health and regulatory decision makers. Without attention to this consideration, there is a real risk that a study will not be designed to resolve critical uncertainties about the performance of a medical product or other intervention. With advance planning, there is the opportunity to identify and align on the study outcomes that are necessary to inform prioritized decision making by the CDC, FDA, and other public health decision makers. FDA can also advise on clinical trial design flexibilities that may be appropriate in the context of a public health emergency.

[2] https://allofus.nih.gov/

Public-private partnerships: While official intergovernmental channels are important for many types of information sharing between FDA and other federal stakeholders involved in an emergency clinical trial enterprise, careful consideration should be given about when to include input from nongovernmental stakeholders as part of the initial protocol planning.

Public-private partnerships can provide a structured, transparent forum for rapid, interactive problem solving about protocol feasibility questions, available data sources, scientific methods, and other important issues that need to be addressed early in the implementation of an emergency clinical trial. To develop clinical trial protocols that can be executed efficiently, it is critical to engage stakeholders from multiple sectors in a way that can address the myriad of scientific, technical, and logistical challenges created by this type of large-scale effort.

Public-private partnerships that enable large-scale emergency clinical trials will help to address some of the challenges associated with rapid development of new clinical trial strategies and protocols in the context of an emergent public health threat. An important example from the COVID-19 pandemic, the COVID-19 Evidence Accelerator, brought FDA and other governmental agencies together with the evidence generation community to develop tools and mechanisms for addressing critical questions that enabled sound regulatory decision making.[3] These included:

- Identifying and prioritizing outcomes that could inform decision making by FDA, including both regulatory decision making and operational decision making, such as resource prioritization.
- Interactive scientific learning, issue spotting, and problem solving around specific issues. For example, how can existing data elements be harnessed for clinical trial data collection? What are the challenges that need to be addressed, such as the challenges associated with capturing measures related to clinical care (e.g., oxygen therapy or ventilation for COVID-19) when the standard of care is rapidly changing?
- Rapid dissemination of information that is foundational to the effective design of clinical studies, such as updated information about disease natural history. For example, what is the appropriate “time zero” to be used for observational studies to address potential sources of bias?
- Facilitating rapid dissemination of learnings and results of studies.

[3] Information about the COVID-19 Evidence Accelerator, including links to research publications resulting from the program, is available on its website, https://evidenceaccelerator.org/ (accessed January 25, 2023).

To build a public-private partnership that can support these goals requires early and meaningful investment of resources, time, and expertise from relevant governmental and non-governmental entities. In order to be prepared for an emergency, a public-private partnership will need to have practiced working together through specific hypothetical use cases or exercises. Through this preparatory work, the public-private partnership should be evaluated to understand how well it is functioning to support likely emergency needs.

Further, large-scale emergency clinical trials should be designed with the goal of earning and retaining the trust of the public in the integrity, objectivity, and transparency of the study objectives, design, and results. Prospective and enrolled study participants must be confident that the study respects their safety, their data, and their contribution to the research effort. To support these objectives, appropriate governance and transparency should be built into public-private partnerships early in their development, in advance of an emergency.

The importance of rapid consensus on clinical trial objectives: Early consensus on study objectives is especially important if the goal is to conduct a study with lightweight data capture methods that minimize the burden on healthcare providers to input data into a traditional study tool, like a case report form. Different study outcome measures can vary widely in the degree of difficulty of ascertaining the outcome from data that is available in the normal clinical care setting.

However, even the most thorough preparation of clinical trial infrastructure cannot anticipate every challenge the evidence generation process creates, including steps that present unique issues depending on the specific nature of the public health emergency (e.g., type of infectious agent).

g. Best practices, including “quality by design” principles, for designing trials so that they capture the data needed without unnecessary complexity that can complicate execution.

Large-scale emergency clinical trials must balance the need for efficiency in data collection with the quality controls necessary to ensure not only participant safety and privacy but also trust in the data by regulatory decision makers and others who rely on the study results to make rapid decisions in an emergency. To meet these goals, an emergency clinical trials infrastructure should develop consensus on the appropriate quality controls as early as possible.

The approach to clinical study quality questions should be informed by the experience of public health decision makers, especially FDA. A retrospective review of clinical data quality issues encountered by FDA during the pandemic may be a practical way to

refine and tailor the clinical research quality principles that should apply to a future public health emergency. For example, what types of quality concerns arose in review of data submitted to FDA during COVID-19? Given the heavy reliance during COVID-19 on decentralized clinical trial capabilities, what were the effects on data quality, participant safety, etc? How can FDA have more information to make risk-based assessments of appropriate clinical trial approaches for future public-health emergencies? To the extent that these learnings are not already reflected in FDA guidance, it will be important to apply them to the context of an emergency clinical research infrastructure.

h. Best practices for designing trials that can enroll vulnerable populations, such as the pediatric population, as needed in particular circumstances.

In the case of pediatric participants, trial sponsors should consider utilizing existing and familiar sites of care, integrating study activities with routine care visits and touch points whenever possible. We address other relevant considerations in the response to 2.b., below.

i. Optimal ways to manage interactions with domestic and international regulatory bodies.

Large-scale studies in the emergency setting will likely have a primary goal of informing rapid regulatory decision-making on, for example, the authorization of a medical product for emergency use. It is critical that the clinical trial infrastructure incorporates input from FDA, and from regulatory agencies in other countries, to the extent that this is feasible and can help ensure that the emergency clinical studies can inform decisions abroad. Regulators have an essential role in informing study objectives, design decisions, data sources, data quality standards, etc. Regulators also should be involved in designing pilot projects to test research and data infrastructure, ahead of an emergency, with realistic use cases. Pre-defined relationships (e.g., public-private partnerships) can help manage and coordinate interactions with FDA and international regulatory bodies.

j. Appropriate entities to handle projecting and tracking enrollment at study sites, monitoring the progress of clinical trials, and data management; whether existing entities could be engaged or adapted to carry out these functions for coordinated, large-scale emergency clinical trials.

A significant number of technology-enabled tools exist to perform clinical trial functions; SignalPath, Verily's Clinical Trial Management System (CTMS), is currently used by a wide variety of health systems to manage critical operational components of research studies. Clinical trial sites supporting large-scale trials in an emergency situation should

have experience utilizing these types of tools and the capacity to deploy them quickly to conduct new trials.

2. Identifying and Incentivizing Research Institutions and Networks; Building Diversity and Equity.

b. Effective ways to increase diversity among study participants and investigators, and to expand clinical research sites into underserved areas.

[Consolidated response to 2.b.] As described recently in a paper by Verily authors,[4] healthcare disparities are driven, in part, by the persistence of inadequate representation of diverse communities in clinical research. Key recommendations to address this issue are summarized below.

Decentralization is an important tool in improving access to clinical trials for diverse populations. It has been made possible by novel digital solutions that allow for remote access for participants. Examples of decentralized elements also include e-consent (i.e., the remote conduct of consenting processes) and digital medicine, which facilitates substantive remote clinical trial participation through mobile clinical trials and remote study visits, data collection, and monitoring.

While the decentralized model can be used to build more diverse clinical trials, it is paramount to deploy patient-centered approaches that account for an individual's preferences for interaction, including combining remote arrangements and availability of in-person physical locations. There may also be a need for in-person interactions to administer certain trial interventions (e.g., tests or adverse event management). Trial sponsors can utilize non-traditional study sites such as community centers, churches or pharmacies to address those needs.

Besides removal of demographic barriers, clinical trial sponsors should address other exclusionary requirements such as those related to health insurance, employment, or residency documentation, limiting participation based on these requirements only if it is relevant to the outcome addressed by the study.

Recruitment issues can be determinate factors in the success or failure of clinical trials, particularly when the goal is to enroll certain high-risk or vulnerable populations. Importantly, recruitment sites should be broadened beyond traditional academic medical centers and health system settings. Efforts to support diversity in clinical trial research

[4] Washington, V., Franklin, J.B., Huang, E.S., Mega, J.L. and Abernethy, A.P. (2023), Diversity, Equity, and Inclusion in Clinical Research: A Path Toward Precision Health for Everyone. Clin Pharmacol Ther. https://doi.org/10.1002/cpt.2804

leadership and staff across these sites will also be important for building trust with traditionally underrepresented trial participants.

For example, the Project Baseline Health Study[5] (conducted by Verily Life Sciences) and the All of Us program (cited earlier in this document) are studies with enrollees that reflect the broader U.S. population. Another study sponsored by Verily, Predictors of Severe COVID-19 Outcomes[6] (PRESCO) (NCT04388813), ensured Spanish speaking trial coordinators were available to support interactions with potential study participants. Study documentation was also available in multiple languages.

Other initiatives, such as the HERO (Healthcare Worker Exposure Response & Outcomes) Registry and HERO Together study (NCT04342806; sponsored by Pfizer), deployed strong remote enrollment strategies and diverse, multi-lingual referral and information touchpoints throughout relevant communities[7] (e.g. pharmacies). Verily supports use of these enrollment strategies that ensure accessibility by diverse and representative populations.

Verily also supports the inclusion of evidence generated from observational/real-world data (RWD) or large-scale pragmatic clinical trials as it is based in routine healthcare delivery. These types of studies can improve cohort size, including from underrepresented populations, and can also be utilized to follow patients longitudinally. Pragmatic trials are another possible solution that allows for more methodological flexibility and can reduce the analytical bias in RWD studies.

Finally, large-scale emergency clinical trials should leverage opportunities to use evidence generated by wearables and other digital health technologies as means to eliminate traditional study burden barriers in all populations and facilitate patient-centered trial approaches.

[5] Arges, K., Assimes, T., Bajaj, V. *et al.* The Project Baseline Health Study: a step towards a broader mission to map human health. *npj Digit. Med.* 3, 84 (2020). https://doi.org/10.1038/s41746-020-0290-y

[6] National Library of Medicine (U.S.). (2020, October). *Predictors of Severe COVID-19 Outcomes.* Identifier CT04388813. https://www.clinicaltrials.gov/ct2/show/record/NCT04388813

[7] https://heroesresearch.org/

1 Executive Summary

ICON plc is a top-two global Contract Research Organization (CRO) with a 32-year history of excellence helping to accelerate the development of drugs and devices that save lives and improve quality of life. At ICON Government and Public Health Services (GPHS), a business unit of ICON plc (described together as, "ICON"), we focus on the critically important mission of population health. We are pleased to respond to the Office of Science and Technology Policy (OSTP)'s Request for Information with our considerations for a national clinical research infrastructure and emergency clinical trials. During the COVID-19 pandemic, ICON supported 26 full-service COVID-19 clinical trials, many of which were initiated at the start of the pandemic when critical factors such as regulatory pathways, clinical research endpoints, and patient populations were unknown and rapidly evolving. We bring these considerations and experience to our OTSP responses and commend the government for these efforts to harness these crucial lessons learned in order to apply to future clinical research. In support of the Pfizer vaccine, ICON worked with 153 sites in the U.S., Europe, South Africa, and Latin America to ensure the recruitment of more than 44,000 trial participants over a four-month period, achieving unprecedented trial timelines while maintaining high standards of quality. We recognize the importance of a variety of contributors providing input to this conceptual emergency research framework and this mirrors our experience working with multiple stakeholders including entities such as the Biomedical Advanced Research and Development Authority (BARDA), the National Institute of Allergy and Infectious Disease (NIAID), the Joint Program Executive Office (JPEO), as well as the Gates Foundation and Gates Medical Research Institute (Gates MRI), and the Coalition for Epidemic Preparedness Innovations (CEPI).

ICON GPHS embraces a culture of ownership in the process of turning molecules to medicine through our mission-driven CRO work. Our work to support and coordinate clinical trials for drug development is highly regulated and driven by a myriad of organizational standard operating procedures (SOPs). As such, we feel the US Federal Government and the OSTP research infrastructure would benefit from the inclusion of a large CRO supported by SOPs and related systems to ensure the efficient management of coordinated, large-scale clinical trials in order to build capacity to address outbreaks of disease and other emergencies. ICON has established access points to clinical sites of all types, whether community-based, academic, or other, as detailed and demonstrated through our completion of 2,988 clinical studies enrolling 844,200+ patients and healthy volunteers at 108,300+ sites globally in the past five years. The advantages of including ICON GPHS include:

(1) The agility and dedication to meet OSTP's current and evolving needs: as a mission-driven division, ICON GPHS is one of only a few large CROs that can meet the compliance requirements and obligations for both the US government and commercial Sponsors. We offer nimble and agile solutions and focused on proactive communication.

(2) The experience and resources of a large company (parent company ICON plc): as a division of ICON, GPHS can access world-class professionals and therapeutic experts, advanced technologies, and vetted strategies to support OSTP's successful clinical trials, supported by the global footprint of a top-two global CRO with a 32-year history reliant on more than 40,900 employees in 110+ offices in 45+ countries worldwide.

(3) ICON's familiarity with the federal government's IDIQ model of working with multiple stakeholders: as a current CRO partner with the federal government on large contracts such as the BARDA Clinical Studies Network for development of medical countermeasures, we understand how decision-making processes unfold within a much larger framework. ICON's role in this context covers clinical trial planning and execution, so while we have clinicians to offer,

we defer to the program's governance body of clinicians and focus on providing value through supporting the management, clinical monitoring, and regulatory compliance for the emergency network.

(4) Robust Standard Operating Procedures (SOPs): as an experienced CRO, we have an extensive history of creating robust International Council for Harmonisation (ICH) Good Clinical Practice (GCP) E6 R2 and Food and Drug Administration (FDA)-compliant SOPs that cover comprehensive clinical development activities to minimize clients' risk through ensuring consistency and compliance across your portfolio. Compliance includes all regulations (applicable statutes such as 21 Code of Federal Regulations (CFR) 312, 21 CFR 812, and 45 CFR 46). Our SOPs are also customized to meet your specific needs.

ICON has undergone a number of regulatory inspections and sponsor audits from both commercial and U.S. Government organizations and our personnel adhere to strict procedures to ensure quality, timeliness, and fiscal responsibility in planning and implementing projects to provide a superior program approach. Our unique advantages minimize risk in execution of clinical programs and ensure ICON adds significant value by supporting OSTP in improving clinical trial emergency preparedness. Given the extensive depth and breadth of the RFI request, we would welcome the opportunity to discuss the content and concepts of our responses in more detail at a future date.

2 Governance for Emergency Clinical Trials Response

ICON supports creating a program-specific governance committee of Subject Matter Experts (SMEs) from each stakeholder group (e.g., government, CRO, pharmacy, and academia) to prioritize research and direct emergency infrastructure preparation while ICON tracks and reports key program information. As a key facet of our suggested governance model, ICON measures program performance according to the metrics of quality, cost, and time and communicates progress and performance in joint governance forums with our clients and stakeholders. ICON regularly reviews study timelines with clients and records key information in meeting minutes to ensure our clients are aware of study progress. Our flexible, in-house project tracking systems will ensure that OSTP is always aware of program status. Communication focus areas include review of Key Performance Indicators (KPIs), process improvement, and risk mitigation as related to delivery, quality, capacity management, and costs.

ICON regularly provides efficient and effective governance structures for large clinical trial contracts that are suitable models for OSTP's emergency infrastructure preparation. Due to our experience as a top-two global CRO—on both complex IDIQ contracts with federal government agencies and contracts with large biopharmaceutical organizations—we understand the importance of the maintaining the highest level of quality standards and flexibility to focus on the unique considerations of interest to all stakeholders. ICON's knowledge of sponsor concerns (e.g., proprietary information) and shared understanding with various government stakeholders (e.g., regarding the importance of regulatory compliance) enables us to provide exceptional clinical trial governance, management, and execution.

ICON acknowledges the importance of known criteria that determine when coordinated and potentially large-scale clinical research is needed to address an outbreak of disease or other biologic incident and the factors that determine the type of study needed, including scope, severity, and location. We recommend these decisions be based on each specific occurrence as discussed amongst the SMEs on the program's governance committee.

As a CRO focused on communication in large clinical research trials with numerous stakeholders, ICON would be happy to implement a centralized portal to facilitate information

access for all stakeholders, including communication of decisions to begin emergency research. For example, our FIRECREST portal provides sites with a secure, role-based central communication hub for access to clinical trial documentation.

Established relationships with validated partner institutions, networks, and sites will be a valuable resource to strategically fill the tracking needs in this emergency research to ensure enrollment and adequate geographic coverage. ICON maintains such established relationships and is in daily communication with our own Global Site Network (GSN) and Healthcare Alliance (HCA) sites to obtain real-time data specific to each protocol, including enrollment projections. Additional information regarding our site networks is provided in Section 3 Identifying and Incentivizing Research Institutions and Networks; Building Diversity and Equity.

It is a CRO's responsibility to recommend target patient populations and site recommendations for the clinical trials we support - we currently perform this activity for Sponsors each and every day. The appointment of SMEs to an emergency trial program's governance committee would provide a key group of stakeholders to approve the target criteria based on the unique emergency or emerging health threat.

ICON recommends relying on an established framework of proven SOPs in overseeing clinical trials. As an experienced CRO with an extensive history of contracting with the both the federal government and private commercial entities, ICON can oversee protocol development while a sponsor organization selects investigational agents. ICON's robust ICH GCP E6 R2 and FDA-compliant SOPs cover comprehensive clinical development activities to minimize our clients' risk. Our SOPs comply with all regulations and provide sufficient flexibility to be customized to meet your specific needs. ICON's SOPs and supporting systems are vetted through their use on hundreds of trials per year to ensure we efficiently execute our sponsors' clinical trials and undergo regular review, on at least a tri-annual basis, and when there are updates to regulatory requirements or accepted international standards.

As a CRO, ICON recommends and regularly executes quality by design through vetted Quality and Project Management Plans to ensure trials capture the data needed without inviting unnecessary complexity. In addition, best practices include verification by our Regulatory Team that trial design meets or exceeds all applicable requirements.

Given the unique nature of trials for vulnerable populations, ICON recommends and relies on internal centers of excellence that supply SMEs who specialize in and provide best practices for unique and specific areas of interest, including centers for pediatric populations and patient engagement. Each center works cross-functionally within a trial network to ensure ICON provides exceptional services suited to each client and research program's specific needs.

Managing interactions with regulatory bodies requires a centralized database and established SMEs. ICON recommends an up-to-date Regulatory Team to keep up with changing regulations and guidance. We maintain Regulatory Team with access to the RegIntelVeevaVault (RIVV) system, a repository of all country-specific regulations, and existing SMEs in each country for immediate update per any regulation changes. We can set alerts for regulatory updates in RIVV for applicable countries for upcoming work.

ICON recommends and operates a sophisticated suite of GCP- and 21 CFR-compliant systems that enable us to manage and administer numerous clinical trials across all phases at scale, including projecting and tracking enrollment, monitoring trial progress, and managing data.

ICON recommends use of centralized repositories based on program need. We regularly work with a number of different vendors who handle data and biospecimen repositories. As one

example, on a BARDA program for Clinical Study Network Medical Countermeasures, we work with a vendor responsible for data services and a separate vendor for biospecimen/biorepository.

ICON recommends that the SMEs on the program's governance committee decide access criteria. As a federal contracting CRO, ICON is able to adhere to a variety of requirements.

3 Identifying and Incentivizing Research Institutions and Networks; Building Diversity and Equity

ICON recommends relying on established relationships to identify institutions and sites. As a top-two global CRO, ICON maintains such established relationships with validated partner institutions and sites and communicates daily with our own GSN and HCA sites to obtain real-time data specific to each protocol, including enrollment projections. ICON's GSN is Accellacare, a merger of two existing site networks, PMG Research, Inc. in the U.S. and MeDiNova in Europe, the Middle East, and Africa. Accellacare sites have access to over eight million patients through their Research Databases and Healthcare Partner Electronic Medical Records. Our sites have conducted over 9,730 trials with no regulatory or legal sanctions. Accellacare sites reduce queries per page by 24% and are 36% faster at query resolution. In addition, our sites have an average of 22% less key protocol deviations per patient per site. Accellacare evaluates and engages clinical trials, including provision of rapid start-up of sites, understanding of the participant journey, strong and innovative recruitment approaches, intensive site program management with fast and effective decision-making to mitigate risks, higher enrollment coupled with higher quality, excellent outcomes from regulatory and sponsor inspections, and high retention levels. These elements are key differentiators that make us clinical trial specialists, not simply specialists conducting clinical trials.

ICON has also worked to engage and develop relationships with the top performing sites globally to ensure the site and participant solution is fully comprehended. This external network of sites is ICON's HCA, with over 45 relationships including site management organizations (SMOs), 100 hospitals, and health care systems in over 20 countries (including closed health care systems). To support these relationships, we provide Alliance Site Members with a dedicated ICON Alliance Single point of contact who are able to function as their internal champions. The benefit is a relationship that delivers consistency with accurate recruitment predictions, and efficient study start up procedures, which require less time for site initiation overall. All of ICON's HCA sites have in place fully executed confidentiality agreements enabling direct exchange of study information and rapid assessments of prospective interest, capability, accrual prospect, as well as top-level protocol reviews. These sites and relationships are able to be leveraged for the OSTP's use and program execution.

ICON agrees that community outreach is an important component to increase diversity and has extensive experience in communications and outreach, providing news articles, speeches, website content, reports, and press and promotional materials for publication in support for program objectives. We have produced approximately 60 speeches and communication materials and supported approximately 40 events supporting diversity. We support local outreach via posters/flyers, information brochures, social media, etc. as well as a broad community launch through partnership with commercial companies and pharmacies with an established customer base as a marketing/communication arm. ICON proposes including a website as a hub of program information that identifies all stakeholders, the mission statement focused on how the program will help the community, and the background for its creation to leverage research in preparation for future emergencies. As an additional outreach effort, ICON recommends marketing this website in pharmacies (e.g., Walgreens) in an easily accessible manner, such as posting a QR code to direct parties the program website.

Decentralized Trials (DCTs) increases diversity and mitigates many of the barriers that impact the prompt collection of high-quality data—a key component for successful trials. They also have lower costs and dropout rates, better enrollment timelines and turnouts than traditional trials by reducing the patient burden by making trial participation more convenient. The DCT and hybrid DCT models also allow the opportunity to broaden the reach into communities that historically have been difficult to engage in clinical research due to location (lack of proximity to traditional clinical research sites), socio-economic factors, etc. Extending this reach will result in greater diversity in clinical trials to more closely mimic real-world settings, producing a more accurate assessment of the safety and toxicity of investigational medical products in populations that form contemporary societies. The data generated from these DCTs are also applicable to general populations, contributing to scientific advances and superior medical products.

As recent examples of our DCT capabilities, ICON worked as a CRO conducting the first registrational fully DCT trial for the Janssen Chief-HF heart failure study in 2019 as well as more recently running the BARDA SNIFF study, which researched longitudinal nasal swabs of adolescents to better understand how the SARS-COV2 virus grows and responds after initial infection. The Janssen Chief-HF study enrolled patients through large healthcare systems and all study-related activities were completed by participants via smartphone app and the use a wearable device. The BARDA SNIFF study was the first U.S. Government-sponsored program to incorporate DCT and ICON helped to ensure participants' immediate safety in the face of the unprecedented health risks COVID brought through successful implementation of a DCT. ICON has also worked on numerous additional non-Government studies that include DCT elements.

An additional innovative approach ICON recommends is adaptive trials. Use of adaptive trial design has rapidly risen as sponsors capitalize on its ability to increase portfolio valuation by protecting good drugs from failure and improve decision-making at critical junctures in the development process. With more than fifteen years of experience in successfully planning and managing adaptive clinical trials, ICON offers design, simulation, and execution of adaptive clinical trials. This provides experts with direct involvement in regulatory agency adoption of adaptive design trials and subsequent agency guidance as well as operational teams and technologies to apply the power of adaptive techniques to drug and medical device trials.

ICON is the only CRO to offer a validated design, simulation, and analysis software platform for adaptive clinical trials. This platform, ADDPLAN, is used by regulatory agencies around the world: FDA (US), EMA (Europe) and PMDA (Japan). An additional technical innovation that supports ICON's design, simulation, and execution of adaptive trials is ICONIK. ICONIK is ICON's platform for advanced data analytics, visualizations, and reporting tools, developed to support centralized monitoring of data and risks on clinical trials as part of a risk-based framework using Spotfire as the data visualization engine. ICONIK enables visual analysis, signal detection, and trend review from the program level down to the individual patient and record level, right across the range of data sources captured on clinical trials today and those that will be more prevalent in the future.

ICONIK integrates data from the EDC, labs, eCOA, IRT, Imaging, wearables, and sensors, and CTMS as standard and can integrate many other datatypes from more niche sources. It has been used on studies since 2012 and has been enhanced continuously since then to support smarter and more targeted approaches for analysis and visualization of clinical and medical risk and trends as part of the risk-based approach. Implementation of ICONIK is associated with 50% lower protocol deviations per site, a 45% reduction in total data queries, and a 56% improvement

in median screening rates for studies. Additionally, assuming a site monitor can get full access to the source notes for an off-site visit, ICONIK provides a reduction of cost per off-site monitoring visit of approximated at 40%.

Key technological innovations that ICON recommends to reduce the number of in-person site visits include telehealth, home health care, direct-to-patient delivery, and using digital health technologies (DHTs, e.g., wearables and other devices). There are a range of DHTs that could be deployed and the specific selection of devices for long-term data capture is driven by study budget, patient acceptance and usability, and the data's regulatory requirements. In addition, direct-from-patient data collection methods—such as eDiaries and ePROs—improve data quality and compliance as the real-time data are available directly from the source.

ICON recommends building on existing programs that target diversity. Our strategy team can cross compare to pre-existing programs to look for targeted diversity. Our Symphony data captures many interactions with the U.S. healthcare system and the longitudinal nature of the Symphony Claims Data will allow for tracking patients over time and observe claims. The Symphony data is an open-sourced dataset that mirrors the U.S. population. Therefore, our data aligns with the actual population, including underserved populations.

As demonstrated on the first-of-its-kind DCT which ICON ran (the Janssen Chief-HF adult heart failure study), ICON encourages and has executed partnerships with commercial and pharmacy chains for patient networks and community access.

At the direction of OSTP, incentives may be provided to participants, institutions, and sites for their time and efforts on this program. ICON’s creation of participation incentives for a study also includes building in incentives for continued retention and participation at specified time points throughout the life of the study or program. We keep participants informed on study and program progress and the impact of their participation in the study and program. This approach has been used successfully in ICON studies and greatly enhance study and or retention.

ICON proposes a website as a hub of program information, including identifying all committed stakeholders, a mission statement to leverage research in preparation for future emergencies, and focus on how the program will help the community.

ICON recommends established relationships with validated sites (such as our GSN, Accellacare, detailed above) to smooth the request and provision of required information.

ICON recommends and provides both regulatory compliance and therapeutic training for specific project requirements and challenges. We can maintain a library of available GCP and protocol-specific trainings on a secure, web-based study portal (FIRECREST) for any and all team members to access and to aid in retraining. FIRECREST is a suite of digital solutions designed to better educate sites and study teams, automate manual tasks, increase compliance, and reduce risk for the OSTP. FIRECREST is associated with increased training compliance (40% fewer protocol deviations per subject visit) and is proven to reduce the cost of trial management, improve data quality, reduce data variability, accelerate enrollment, and increase site and study team satisfaction and engagement. The solution is currently driving trial performance on close to 1,000 active studies for 174 sponsors and used by over 549K users in 143 countries at 31K research sites. FIRECREST supports best-in-class training at the protocol level.

4 “Warm Base” Research

ICON agrees that "warm base" clinical research adds value to the emergency infrastructure preparation. The government's utilization of the 'warm base' model is evident in other research frameworks, including IDIQ contracts that ICON is actively supporting - BARDA's Clinical Study Network for medical countermeasures, the NIAID Comprehensive Rapid Response

network, and the NIAID Early Phase Clinical Trial network. We recommend the SMEs on the program's governance committee decide the disease areas/conditions and locations for "warm base" studies. To enhance the overall evidence collected from an emergency clinical trial program, during the consenting process, our proprietary tokenization process can apply a unique identifier—our Synoma patient key—to all participants in the OSTP emergency infrastructure preparation studies. This allows OSTP to enhance the primary data collection for the study with bidirectional longitudinal secondary data for the cohort (including pharmacy claims, medical claims, EMR, etc.) for long-term follow-up and health outcomes.

We recommend the SMEs on the program's governance committee decide the best implementation of "warm base" research to provide training to sites. Additionally, ICON can maintain a library of available GCP and protocol-specific trainings on a secure, web-based study portal (FIRECREST, further discussed in Section 3 Identifying and Incentivizing Research Institutions and Networks; Building Diversity and Equity).

5 Emergency Master Agreement

ICON agrees to the importance of implementing an agreed-upon Emergency Master Agreement prior to conduct of work to facilitate the emergency preparation infrastructure program's success. For example, ICON routinely enters into similar agreements, called Master Service Agreements (MSAs), which provide basic terms for larger contracts and may include such topics as data ownership rights; expectations regarding accessibility of information (including proprietary and confidential information); publication rights for trial data; use of a single, centralized Institutional Review Board (IRB) to expedite clinical research; control of the study drug; etc. While the MSA covers such basic contract terms, each unique trial project is attached via a work order for specific study. We recommend and maintain relationships with central IRBs and advocate pulling IRBs into the governance committee as stakeholder to research framework so they can pivot their resources should the emergency network be turned on and require an IRB.

6 Identifying Viable Technical Strategies for Data Capture; Gathering Information about a Potential Data Capture Pilot

In our experience as a CRO, data capture and management are key components of registrational clinical trials, as they represent our deliverable to the FDA to prove the safety and efficacy of trial products. Historically, data capture has focused on maintaining information obtained from patients in an Electronic Data Capture (EDC) system, but ICON recommends newer means of populating EDC systems, including patient wearables and Electronic Medical Records (EMRs) from hospital systems to ensure a direct link from patient data and EDC platform.

ICON submits for consideration building the study database using Rave™, an industry-leading EDC software application provided by Medidata Solutions. Rave is accessed via a secure web browser, facilitating clinical data collection and study management. It is a highly scalable and stable platform with proven capability to conduct clinical studies with 120,000+ subjects and 3000+ sites and supported by Medidata's 24*7 Tier-1 Global Help Desk. As a cloud hosted EDC system, it ensures high availability (99.5% system uptime) and real-time access to data extracts. Key functionality of the system includes capabilities to screen and enroll subjects; enter and manage form, comment, and visit data; issue, answer, and close queries; source verify forms; freeze and lock forms; sign forms and case report books; and create reports and analyze data.

ICON has a long-standing relationship with Medidata for Rave EDC services dating back to 2004 and has successfully leveraged its tools on countless programs. With over 18 years of experience in Rave core functionality, our expertise spans Rave 5.5, 5.6, and 201x product lines, across multiple therapeutic areas and clinical phases. ICON's system-aligned team of certified

Rave Programming Leads averages more than 12 years of clinical research experience. ICON has 30+ members of the Global Rave Clinical Programming team that are trained and certified to build. ICON is accredited in Rave, Targeted Source Data Verification (TSDV), Coder, ePRO, Randomization and Trial Supply Management (RTSM), Rave Imaging, and Clinical Trial Management System (CTMS), with a pending accreditation in Safety Gateway.

7 International Coordination and Capacity

ICON recommends designing trials that facilitate foreign-run trial network participation. As a provider of drug development solutions and services to government, academic, pharmaceutical, biotechnology, and medical device industries worldwide, ICON provides expertise in global strategic development, management, operation, and analysis of programs that support clinical development. In the last five years alone, we have conducted trials on all earth's inhabited continents, including 6 countries in North America, 5 countries in South America, 35 countries in Europe, 18 countries in Africa, 21 countries in Asia, and 2 countries in Australasia.

ICON recommends relying on established relationships, such as our GSN, Accellacare, that provides the capability to search across multiple sources to rapidly identify high-quality sites with the right profile. We provide our sponsors with experienced Site Identification Leads and Specialists to ensure optimal management/reporting and site contact/follow-up/qualification. We are able to streamline the site identification process to facilitate site participation using a protocol synopsis/targeted study summary and a shortened, focused feasibility questionnaire (FQ) sent at the same time as an electronic Confidentiality Disclosure Statement (eCDS) embedded as part of the FQ. We will query both our in-house and external investigator databases for experienced vaccine centers in selected countries. In addition, any prior performance on ICON studies will be reviewed to assess their potential for participation in advance of reaching out to them.

In our experience responding to COVID-19, ICON conducted a top-level blinded outreach globally to solicit preliminary site interest both for COVID vaccine and treatment studies and found a high interest (~90%) among sites contacted for such studies. ICON can leverage this information in addition to our other site ID tools to pre-identify potential sites to facilitate the overall site ID process for future emergencies.

ICON has completed 12,988 clinical studies enrolling 844,200+ patients and healthy volunteers at 108,300+ worldwide in the past five years. Our worldwide experience highlights the need to work with numerous regulatory authorities, flexible and differing processes, and unique considerations for product importing across countries. Specific recommendations can be provided when details of the study specifications and locations are fully flushed out.

Given the G7 Charter's collaboration with the WHO, GloPID-R, GHSI, CEPI, etc., we believe policies and procedures may already be in place to track initiatives and harmonize efforts, requiring only a focus on coordination for this program initiative. Given the large program experience and presence in numerous countries, ICON is prepared to coordinate with the G7 Charter team to track and harmonize research initiatives. If additional tracking is required, we will help to build an umbrella system based on our extensive experience as a CRO, to incorporate data trends and match patient population to bring it all together, following all applicable laws and regulations.

January 27, 2023

Arati Prabhakar, PhD, MS
Director
Office of Science and Technology Policy
Washington, DC 20500

RE: Notice of Request for Information on clinical research infrastructure and emergency clinical trials (87 FR 64821)

Dear Dr. Prabhakar:

On behalf of the American College of Obstetricians and Gynecologists (ACOG), representing more than 60,000 physicians and partners dedicated to advancing the health of women and all those seeking obstetric and gynecologic care, thank you for the opportunity to help inform the development of a U.S. clinical trials infrastructure that can better respond to outbreaks of infectious disease or other public health emergencies. As obstetrician-gynecologists, we especially urge you to take steps that will guarantee that the infrastructure prioritizes the safe inclusion of people who are pregnant and lactating in clinical research during times of emergency, consistent with the mission of the Office of Science and Technology Policy (OSTP) "to maximize the benefits of science and technology to advance health, prosperity, security, environmental quality, and justice for all Americans."[i]

The COVID-19 pandemic magnified deficiencies in our existing clinical trials infrastructure, negatively impacting the development of COVID-19 diagnostics, vaccines, and therapeutics. For pregnant individuals, those deficiencies contributed to their exclusion from critical COVID-19 research and their subsequent absence from early vaccine allocation determinations, resulting in delays in many pregnant individuals accessing COVID-19 vaccines, and very likely contributing to avoidable loss of life.

ACOG has long advocated for the safe inclusion of pregnant individuals in research, and for nearly a decade has encouraged reframing the classification of pregnant individuals in research trials as a "scientifically complex" rather than a "vulnerable" population.[ii] We also recognize that research in pregnant individuals presents specific scientific, ethical, and legal complexities.[iii] Yet the existence of these complexities is not reason to automatically exclude pregnant individuals from research. Consistent with recent infectious disease outbreaks, including H1N1 and COVID-19, we know that pregnancy is a time of potential increased risk for severe disease, necessitating special considerations for the care and treatment of pregnant individuals. This past experience underscores that, especially in times of infectious disease outbreaks, it is critical that we consider the imperative of protecting pregnant individuals *through* research rather than *from* research, and that an effective infrastructure would prioritize this population.

It is therefore essential that OSTP incorporate people who are pregnant and lactating into every aspect of planning for an improved clinical research infrastructure, including:

- Prioritizing pregnant and lactating people in the development of clinical trials protocol;
- Developing best practices for designing trials that incorporate pregnant and lactating people and for recruiting these populations;

- For trials funded in whole or in part by the federal government for products that may be used by pregnant and lactating people, requiring a written justification if they are excluded;
- Leveraging existing obstetric clinical trial networks, such as the Maternal-Fetal Medicine Units (MFMU) Network;
- Incentivizing or providing additional financial support to clinical trial sites that enroll people who are pregnant and lactating; and
- Ensuring that any common Institutional Review Board includes members with expertise in obstetrics and to document justification for excluding pregnant or lactating people from clinical trials based on regulatory requirements outlined the Federal Policy for the Protection of Human Subjects (the "Common Rule").

In addition to the recommendations outlined above, the Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC) has released a series of recommendations and an implementation plan that contains detailed recommendations to advance the inclusion of pregnant and lactating people in clinical research.[iv] We recommend that OSTP review and incorporate, as appropriate, the PRGLAC recommendations.

We believe that by incorporating the unique needs of pregnant and lactating populations into the development of an improved clinical trials infrastructure, OSTP can guarantee that pregnant and lactating people are protected from health threats in a future pandemic or other health emergency. We look forward to working with you on this important issue. Please don't hesitate to contact Rachel Tetlow, Federal Affairs Director, at rtetlow@acog.org if we can provide any additional information.

Sincerely,

Christopher M. Zahn, MD
Col (Ret), USAF, MC
Chief, Clinical Practice
and Health Equity and Quality

[i] https://www.whitehouse.gov/ostp/
[ii] Ethical considerations for including women as research participants. Committee Opinion No. 646. American College of Obstetricians and Gynecologists. Obstet Gynecol 2015;126:e100–7.
[iii] Ibid.
[iv] The 2018 Report to the Secretary of Health and Human Services and Congress of th Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC) and the 2020 PRGLAC Report Implementation plan can be found at https://www.nichd.nih.gov/about/advisory/PRGLAC.

Response to Emergency Clinical Trials RFI

Jan 27, 2023

Submitted to *emergencyclinicaltrials@ostp.eop.gov*

by

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Background:

RTI International is an independent nonprofit research institute dedicated to improving the human condition. One of our areas of expertise is biostatistics, data management, program operations and regulatory support for clinical trials and observational studies with long-term follow-up. RTI is the Data Coordinating Center (DCC), Administrative Coordinating Center (ACC), or Research Coordinating Center (RCC) for many US and international clinical trial and observational studies research networks or individual studies funded by NIH, DoD, PCORI, DTRA, CDC, and various research foundations. https://www.rti.org/service-capability/coordinating-centers-multisite-studies.

Highly relevant to this RFI on preparedness for clinical research in future pandemics, RTI is the Administrative Coordinating Center for NHLBI's CONNECTS clinical trial program for potential COVID-19 therapies (https://nhlbi-connects.org), NIH's Researching COVID to Enhance Recovery (RECOVER) Observational Studies (https://recovercovid.org), NIH RECOVER-CT program for clinical trials of potential PASC therapies RECOVER Clinical Trials Announcement 10.31.22 (recovercovid.org), and the Coordinating Center for NIAID Centers for Research in Emerging Infectious Diseases global surveillance and outbreak research network (CREID, https://creid-network.org/).

1. Governance for emergency clinical trials response.

a. Descriptions of models that could be used to establish a U.S.-level governance structure for emergency clinical trials.

- The CONNECTS network-of networks model, by which standing funded NIH/NHLBI networks of sites collaborated to design and implement trials, was an effective way to rapidly convene experienced multidisciplinary researcher teams to plan and implement trials quickly.
- Within that framework, the NIH governance model for CONNECTS and RECOVER, by which many decisions were reviewed and approved at high levels within NIH, at times was not fast nor flexible enough because many decisions had to await approval from top levels (often after first obtaining peer and expert approval by various committees). The internal NIH approval process regularly slowed down start times. However, few proposals/plans were not approved.
- One additional lesson we have learned on RECOVER is the importance of vision and direction from the top to ensure a large research network is working towards the same goals. There are many benefits of maintaining a minimum necessary size of network leadership and decision makers. Building consensus among too many investigators empowered with decision making can cause significant delays in action and if not achieved, may jeopardize the development of an effective research protocol that addresses the public health needs. A more successful strategy would be to strategically select an appropriate minimum size of project thought leaders/decision makers, followed by a framework of simplified and speedy government approval.
- From the following article, example global partnerships include H3Africa, GISAID, GA4GH, EBI/EMBO, CERN, GIP. The article also discusses intellectual property issues and lessons learned from Human Genome Project. nih.gov/pmc/articles/PMC7292646/

b. Criteria that should be applied in determining when coordinated and potentially large-scale clinical research is needed to address an outbreak of disease or other biological incident,

- Any disease that is rapidly infecting a large portion of the population with significant morbidity and mortality should be a trigger for a large scale coordinated response.
- We must ensure that the populations at highest risk are included in clinical research.
- Relevant criteria:
    a. if the disease appears to have highly variable phenotypes, requiring a large sample size to identify the full range of symptoms and phenotypes or to study individual subtypes of the disease.
    b. if the disease has highly variable effects/symptoms.
    c. If little is known about the disease expression
    d. If no known effective treatments are available.

c. factors relating to the outbreak or incident (*e.g.,* scope, location, severity) that should be considered in determining what types of studies are needed.

- Who is vulnerable, where are they located, do they have access to health care, are there uniquely vulnerable populations, what are the economic impacts of the disease for people and communities. Is it a new pathogen, an unknown pathogen, emerging or re-emerging pathogen? Do treatments exist? Do diagnostics exist? Do vaccines exist?

e. Mechanisms for tracking institutions, networks and sites that might be able to participate in emergency research, to ensure adequate potential for enrollment and adequate geographic coverage, domestically and internationally.

- Understanding the federally funded clinical trials landscape in the United States is a critical requirement to being prepared for emergency clinical trials research. Keeping an active inventory of trials, sites, populations, geographic coverage, equipment, access to supplies and staff, biospecimens collected, etc. ensures that we have the information to intentionally plan, develop, and keep warm the necessary infrastructure to mount an effective and equitable clinical research response. The inventory should include clinical trials and networks funded across the US government. Keeping the information current should be a requirement of receiving funding for clinical research projects. With a live inventory, we can routinely assess the infrastructure to identify gaps and weaknesses and focus resources there. Measuring and monitoring strengths and weaknesses of the system over time should be incorporated. This will ensure accountability to advancing the clinical trials infrastructure for preparedness and response to future outbreaks, epidemics, and pandemics.
- We can practice launching emergency clinical research to identify stress points or bottlenecks and work in advance to mitigate them. We can build out communications strategies to keep networks connected, collaborative, dynamic, and inclusive. Recognizing what of the infrastructure is possible to scale or not is also imperative. We can prototype, test, and build out Memorandum of Understanding, Emergency Use Simple Letter Agreements, Material Transfer Agreements, and Data Sharing Agreements.
- Targeting and developing community-based hospitals and sites treating high proportions of underserved populations is imperative. A national database of prepared emergency clinical

trial sites could identify gaps through comparison to percentage of underserved populations or rates of excess mortality in other outbreaks. This information can inform programs to build and pre-position clinical trial infrastructure in these locations.

- Building out grants and contracts programs with requirements for intentionally partnering to advance representation (geographic, population), community partners, minority junior investigators, etc. should be part of growing the clinical trials infrastructure.
- In the international setting, much work needs to be done to advance collaboration and democratizing and decolonizing global health.
- The CREID Network, coordinated by RTI, has 10 US or France-based research centers with 80+ research sites in 30+ countries around the globe where emerging and re-emerging infectious disease outbreaks are likely to occur. To launch the Network, the Coordinating Center performed a comprehensive inventory of Network site research studies and cohort availability, research experience, laboratory equipment and assay capabilities, site infrastructure capabilities, and site outbreak response readiness. A scalable data management structure was established by the RTI Coordinating Center using a secure, cloud-based storage system and is available to all Network members and NIH via secure private portal with user friendly dashboards. This database availability boosts collaboration across the Network and improves Network members' ability to rapidly pivot research efforts and resources to support future outbreaks. These resources have proven invaluable to rapidly synthesize information for outbreak research response, including when tasked by NIAID to support research efforts for a chikungunya outbreak in Cambodia, early SARS-CoV-2 variants, the 2022 Monkeypox virus (MPXV) outbreak, and the recent Ebola outbreak in Uganda. CREID is an excellent example of collecting and maintaining relevant information for emergency response preparedness and enabling quick access to address key emerging questions.
- As the CONNECTS, RECOVER and RECOVER-CT Administrative Coordinating Center (ACC), RTI provides a consolidated web source for tracking status of potential and contributing clinical research sites (including GIS mapping of location, and study enrollment by study which together provide ability to report gaps and overlaps across NHLBI trials). The database was based on existing NHLBI networks and has been continually updated with new sites identified by collaborating CROs or investigators. This NHLBI-level hub provided efficient real-time information sharing to government and study leadership, including Operation Warp Speed. Access to real-time information about progress provides sponsors, decision makers and researchers with the ability to nimbly adjust to changing conditions.
- For future pandemics, consolidated web reporting of national-level site readiness (database of academic/private/government institutions listing contacts and specialties) and status of major pandemic clinical trials across government institutions following the models for CREID and CONNECTS would support information sharing and identify gaps and excesses on a national level. An OTA-awarded non-government institution could maintain such a web database and reporting tool, at the ready for future needs, seeded with site lists from the recent major COVID trials.
- To enable maximum data sharing across pandemic studies, a requirement for DCC/CCC/site funding could be to provide secure API access to the key data elements. This would ensure

data is discoverable and accessible and would greatly simplify the data sharing process to various entities charged with consolidated real-time reporting, thereby getting information to decision makers more effectively.

g. Best practices, including "quality by design" principles, for designing trials so that they capture the data needed without unnecessary complexity that can complicate execution.

- On CONNECTS, we found that adaptive platform trials designed by multi-disciplinary expert committees with chapters for new agents added over time was remarkably efficient.
- In future pandemics, use of standard endpoints and data definitions across studies is imperative to make studies compatible, combinable, and comparable. Standardization of endpoints was achieved for some CONNECTS trials, yet was not available up-front as COVID was new, and outcome definitions were not widely agreed upon at the time.
- Use of standard case report forms (CRFs) or other data collection instruments across different yet related trials (same data items, same naming and formatting conventions) is imperative to support quick start-up as well as prompt data sharing at study completion. On CONNECTS, a rigorous set of data standards and common data elements were developed (CONNECTS common data elements) yet trailed the start of the initial trials. Data harmonization programming was required at the back end, yet all study data was standardized prior to submission to NHLBI BioData Catalyst for public sharing, supporting ease-of-use of the study data for the broader scientific community.
- Protocols need to be able to change flexibly, to add or modify data items as more is learned about a new illness
- The CONNECTS unblinded trial of existing medications (ACTIV 4A) vs standard of care was much easier and cheaper to implement than a placebo-controlled trial with less site burden. The study achieved meaningful results with mostly robust enrollment. The benefits of open-label trials should be evaluated in urgent pandemic settings.
- Obtaining informed consent with innovative technology such as electronic signatures and other electronic aids is necessary to minimize burden and disease exposure for scarce research staff during a pandemic. Such devices need to be in common use on all clinical trials to be usable in an urgent pandemic setting.

j. Appropriate entities to handle projecting and tracking enrollment at study sites, monitoring the progress of clinical trials, and data management; whether existing entities could be engaged or adapted to carry out these functions for coordinated, large-scale emergency clinical trials.

- For CONNECTs and other NIH-funded large COVID trials, clinical trial Data Coordinating Centers (DCCs) from academic and not-for-profit organizations and Clinical Coordinating Centers (CCCs) at research hospitals completed these tasks for each individual trial as is standard for any trial. On CONNECTS, the Administrative Coordinating Center (ACC, RTI International) assisted NHLBI and the Steering and Executive Committees in oversight of the CCCs and DCCs and was responsible for program-wide tasks.
- In a large pandemic response, there may be concern for capacity of experienced DCCs and CCCs. Nearly all top-notch groups contributed to COVID trials, by shifting research priorities

and staff, sharing leadership roles of large COVID trials across institutions, and/or sub-contracting components to for-profit entities. The standard NIH application, review, and award process was ***substantially*** sped up using the OTA mechanism. On the other hand, we found success of the trials was highly depended on the experience, capacity, leadership, flexibility, and innovation of awarded coordinating centers. It is imperative that such entities be evaluated/vetted prior to award of emergency trials. Once the CONNECTS ACC was in place, we conducted vetting on behalf of NHLBI. Unfortunately, some trials were already awarded prior to the setting up of the vetting process. For future pandemic preparedness, we recommend that government procedures for prompt yet rigorous selection of Administrative-, Data-, and Clinical- coordinating centers for national-level trials be in place to maximize start-up and quality. Pre-vetting and a standing database of such entities along with their capacity and areas of expertise would be an excellent helpful tool.

- Experienced CROs (also vetted by the ACC) were contracted by some CONNECTS trials to add sites and conduct site monitoring. We found that established CROs added needed capacity of site identification/contracting/oversight and CRO teams worked collaboratively, but in general CROs were much less able to act *flexibly* and their work models for collaboration and budgeting/pricing were too rigid. Flexibility is a key component of urgent pandemic research. Their cost was also substantial relative to the not-for-profit and academic sector.
- As the CONNECTS, RECOVER and RECOVER-CT Administrative Coordinating Center (ACC), RTI provides a consolidated web source for tracking enrollment both within- and across program studies, including real-time access to enrolled participants, filterable by demographics (age, gender, race, ethnicity), geographic/site location, study, study therapeutic arm for adaptive trials, indicators of data quality, etc. These real-time interactive dashboards effectively get consolidated information to decision makers and also support study operations to diagnose bottlenecks in site startup (e.g., IRB delays, activation issues) and communicate actual versus expected enrollment at the site level, allowing study coordinators to respond quickly to concerning trends.

k. Appropriate ways to structure a data repository and a biorepository for emergency clinical trial data and specimens. As noted above, one potential model would be to collect data and biospecimens in centralized repositories. We would also appreciate input on whether existing entities could be engaged or adapted to handle these repository functions.

- CONNECTS trials are all (or will be) available for sharing through NHLBI BioData Catalyst, using common data elements (CONNECTS CDEs)
- Maintaining lab samples from large trials in central biorepositories is efficient. However, samples do not need to be all in the same location. Virtual biorepositories, which are a database of available samples combined across numerous studies or laboratories are a powerful tool to compile smaller sets of samples into a more useful resource for mechanistic research. To be an effective fast sharing method, MTAs and DTAs across institutions need to be simplified, standardized, and coordinated.

- RTI is currently working with NIH to develop a virtual biorepository of remaining samples across the ACTIV trials. This model could easily be expanded.
- A recent research article on this topic is: medrxiv.org/10.1101/2023.01.17.23284659v1

3 "Warm Base" Research.

- CONNECTS collaboration of standing NHLBI-funded networks was highly successful and was in fact a "warm base" research model.
- NIAID's STRIVE is an example of a plan to have warm-based acute lung injury research in place for the next respiratory pandemic leading to hospitalizations.
- NIAID's CREID Network is another example of "warm base" global infectious disease research. The cooperative agreement funding mechanism is designed such that investigators can pivot funding to address priority pathogen outbreaks at the request of NIAID. Core components of the Network Vision are to: 1) conduct innovative research to expand knowledge of emerging and re-emerging infectious diseases and better prepare to respond to outbreaks and pandemic threats; 2) establish a collaborative, strategic, and preemptive research Network to ensure coordination of efforts for outbreak preparedness and global health security; and 3) develop and expand flexible domestic, regional, and international capacity and readiness to efficiently undertake research in response to EID threats.
- Other examples include NIH Centers of Excellence for Influenza Research and Surveillance (CEIRS). They have as a mandate "Although CEIRS is primarily focused on influenza, the network also will study SARS-CoV-2, the virus that causes COVID-19, and other emerging viruses of pandemic potential" CEIRS-influenza-response-plan.
- Perhaps development of further types of networks should be evaluated, especially ones that focus on building and maintaining capacity for research in *rural and underserved communities and locations not traditionally participating in research* such as community-based hospitals and clinics.
- Networks cannot be idle to be prepared – active multi-disciplinary collaborate research that can be de-prioritized in a pandemic is essential.

4. Emergency Master Agreement

- A well-accepted streamlined master agreement is critical. On CONNECTS, initial contract execution with a site was not fast enough due to site negotiations of legal terms. A paradigm shift to a pre-determined nationally accepted set of terms is needed for all multi-site clinical research. Often contract negotiations can take months, stymieing enrollment potential, un-necessarily increasing costs and wasting resources at a national level.
- In a pandemic research situation, contract execution and modification must be *fast and flexible* to address changes in trials in response to pandemic changes and new knowledge.

The NIH OTA mechanism was implemented on CONNECTS. All funds flowed from NHLBI to the ACC at RTI, then from RTI to DCCs and CCCs and in turn to network leads and then sites. From June 2020 to Dec 2022, the CONNECTS OTA was modified over 50 times, exemplifying the speed and flexibility of this mechanism. As the ACC, we provided substantial contracting and finance tracking staff, and developed best practices and SOPs for overseeing and tracking the invoices of our subs. Similar effort was also required from each DCC/CCC sub-OTA. The FTE and expertise needed for contracts and finance/invoicing experts in conducting emergency trials is a vital component that must not to be overlooked in preparedness planning for future health crises.

iii. *Use of a single IRB* across all participating trial sites. As a related point, it would be helpful to get feedback on whether an IRB should be established that is primarily devoted to emergency clinical trials.

- Use of a single IRB is best practice and should absolutely be done for future pandemic trials. It is imperative that experienced sIRBs prioritize future pandemics, as they did for COVID. A new sIRB entity that functioned only for emergency situations would not, in our opinion be an effective model. On the other hand, it would be very helpful for established, experienced and reliable sIRBs to have pandemic response plans in place, so they maintain a state of readiness.
- COVID trials stressed the workload of existing sIRBs, and more high-quality national level sIRBs are needed.
- Since CONNECTS adaptive protocols were frequently updated by design, informed consent forms also were updated, and the requirement for the sIRB to review each site's individual updated consent was a rate-limiting step that clearly slowed enrollment. A more streamlined approach to IRB reviews of individual site document updates is imperative for all clinical trials, not just emergency settings.

6. International coordination and capacity.

Designing the overall domestic emergency clinical trials effort in a way that coordinates with international clinical research efforts. It would be helpful to receive comments on how to facilitate the participation of foreign-run clinical trial networks and other foreign bodies in coordinated, large-scale emergency clinical trial protocols initiated by the U.S.

While there are many approaches to this, two suggestions:

- Engage trusted multilateral entities such as WHO or Africa CDC or philanthropy (BMGF, Wellcome Trust, etc.) or NGO's such as CEPI/GAVI to support coordination.
- Design domestic emergency clinical trials in collaboration with international clinical research efforts from the start. In so doing, build partnership and collaborations in advance.

-- END--

ConnectedHealthInitiative

January 27, 2023

Ms. Grail Sipes
Assistant Director for Biomedical Regulatory Policy
Office of Science and Technology Policy
Executive Office of the President
1650 Pennsylvania Avenue NW
Washington, D.C. 20504

RE: ***Connected Health Initiative Comments to the White House Office of Science and Technology Policy on Clinical Research Infrastructure and Emergency Clinical Trials [87 FR 71368]***

Dear Assistant Director Sipes:

The Connected Health Initiative (CHI) writes to provide input to the White House Office of Science and Technology Policy (OSTP) in response to its request for input on clinical research infrastructure and emergency clinical trials.[1] CHI appreciates OSTP and National Security Council's partnered efforts to ensure that coordinated and large-scale clinical trials can be efficiently carried out across a range of institutions and sites to address outbreaks of disease and other emergencies.

CHI is the leading effort by stakeholders across the connected health ecosystem to responsibly encourage the use of digital health innovations and support an environment in which patients and consumers can see improvements in their health. We seek essential policy changes that will help all Americans benefit from an information and communications technology-enabled American healthcare system. CHI is a longtime active advocate for the increased use of new and innovative digital health tools in both the prevention and treatment of disease, specifically regarding clinical trials and investigations. For more information, see www.connectedhi.com.

Digital health technologies (DHTs) are radically improving the American healthcare system and will continue to do so.For example, mobile app-enabled telehealth and remote monitoring of patient-generated health data continues to represent the most promising avenue for improved care quality, reduced hospitalizations, avoidance of complications, and improved satisfaction, particularly for the chronically ill. CHI is a longtime supporter of modernizing and streamlining today's regulatory system to enable leveraging the full potential of device software functions controlling, or part of, a

[1] 87 FR 71368.

hardware device (i.e., Software in a Medical Device, or SiMD) and for devices that are not part of a hardware device (i.e., Software as a Medical Device, or SaMD). A governance infrastructure that empowers providers to choose the best technology and cloud services to innovate within the health sector is critical to advance DHTs.

Digital health technological advances in software applications can vastly improve many facets of clinical trials, strengthening the infrastructure necessary to address disease outbreaks like COVID-19 and other public health emergencies. While mobile apps hold the potential to revolutionize the effectiveness of clinical trials, these solutions are ineffective without sufficient racial and ethnic representation in the data generated from the underrepresented groups that intend to use the medical device. These advances also help bridge the racial divide in representation by aiding in participant recruitment and continued engagement, collecting data, and supervising clinical trial sites and investigators. CHI recognizes that people of color are historically excluded from various facets of the healthcare system and appreciates the OSTP's examination of the changing and increasingly intricate clinical trial enterprise and its crucial role in medical product development.

Broadly, CHI encourages OSTP to partner with trusted organizations committed to equity and diversity, and private sector clinical trial sponsors to improve community outreach. Distrust in the healthcare system is prevalent among many underrepresented communities due to structural barriers to accessing healthcare and deep-rooted perceptions of physician bias. Providing a platform for widely recognized and respected community advocacy groups to provide their views, review educational materials, and eventually promote studies they deem helpful should be a priority.

DHTs are critical for supporting coordinated and large-scale clinical trials conducted across a range of institutions and sites to address outbreaks of disease and other emergencies. Traditionally, in the context of clinical trials, there has been a limited use of DHTs that leverage patient-generated health data (PGHD) due to the costs associated with distributing, connecting, tracking, and maintaining mobile devices during an investigation. With the revolution of smartphone adoption, clinical investigations can now largely discard these concerns, particularly when embracing the "bring your own device" (BYOD) model. Such models may utilize specialized instruments as accessories to smartphones/tablets/etc., enabling a much more complete evaluation of a patient's condition across a diversity of types of data and use cases. The benefits of the full range of DHTs available today include:

- The ability to attain PGHD for data management in real time;
- Increased authenticity of patient-reported outcome data, particularly when such data is aggregated directly from sensors collecting PGHD (i.e., the trial participant is bypassed in the reporting process);
- Enhanced subject retention and subject involvement in the clinical trial due to the ease of reporting PGHD through smartphones or tablets as well as the ability to access this data;

- Reduced training costs, as smartphones are widely adopted and typical subjects will already be trained on how to use their own devices;
- Use of any device, whether a phone at work or a tablet at home, to access the data in a continuous manner, with data interoperability based on open and consensus-based standards (these standards include: the Continua Alliance's Design Guidelines,[2] Health Level 7 [HL7],[3] ISO 12052 [Health informatics -- Digital imaging and communication in medicine including workflow and data management],[4] and the Integrating the Healthcare Enterprise [IHE] initiative[5]);
- The removal of geographic restrictions from trials and investigations allowing
- access to a more diverse set of trial subjects than would otherwise be possible; and
- Reduced maintenance and support costs for sponsors.

The FDA has consistently demonstrated its willingness to embrace advanced technology and connectivity in the healthcare continuum.[6] However, in the context of clinical investigations, a lack of clarity from the FDA regarding the use of DHTs has reduced uptake. Given the rapid development of DHTs, FDA guidance that will facilitate the use of DHTs in a clinical investigation as appropriate for the evaluation of medical products is necessary and timely and will greatly assist Independent Review Boards (IRBs) conduct investigations of non-significant risk under 21 CFR Part 812. Not only is this modernization of FDA guidance good public policy, but it would also be consistent with Congress' goals in the Food and Drug Administration Safety and Innovation Act of 2012 to promote innovation, protect patient safety, and avoid regulatory duplication.[7] FDA's efforts to enable the responsible use of DHTs will also assist in bridging the digital divide and providing needed disease prevention and treatment to America's most vulnerable citizens, in alignment with the Administration's priorities for eliminating disparities in healthcare.

To support its goals improving the U.S. clinical trials infrastructure and improving the ability to carry out emergency clinical trials, we strongly urge OSTP and the NEC to:

- Advance Guidance on the Use of Digital Health Technologies in Clinical Trials: Support the FDA's rapid finalization of its guidance on the use of DHTs in clinical investigations.
- Explore and Support Bring Your Own Device (BYOD) Capabilities: We urge OSTP and NEC to further explore the BYOD model. The BYOD model, whether using mobile apps and/or accessories to a mobile device, holds great potential to

[2] http://www.continuaalliance.org/products/design-guidelines.
[3] http://www.hl7.org/implement/standards/index.cfm.
[4] http://www.iso.org/iso/iso_catalogue/catalogue_tc/catalogue_detail.htm?csnumber=43218.
[5] http://www.ihe.net/About_IHE/.
[6] *E.g.*, U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY AND FOOD AND DRUG ADMINISTRATION STAFF, MOBILE MEDICAL APPLICATIONS (2015), available at http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM26 3366.pdf.
[7] *See* P.L. 112-144 (Sec. 618).

increase efficiency, improve data accuracy, provide real-time access to data, result in greater study participant investment, and break down geographic barriers to participant pools. BYOD devices that utilize proper risk management techniques (including building security into a mobile app from its inception and the use of encryption) along with participant training will greatly improve the integrity of the trial, and can easily provide novel clinical endpoints sponsors and investigators need in standardized formats through the use of application programming interfaces (APIs), software programs that allow for the automated exchange of data between systems, and positioning the sponsor to nimbly address challenges (e.g., a mid-trial device switch by a particular participant for any reason).

Relatedly, CHI continues to support FDA updates to its definition and scoping of DHTs in clinical trial guidance currently under development to address when a DHT is a medical device that has a software function that is not subject to Part 812 per Section 520(o)(1) of the Food, Drug & Cosmetic Act.

- Flexibility in Use of DHTs: OSTP and NEC are encouraged to take an outcome-based approach that is as agnostic to specific technologies and processes as possible. CHI urges OSTP and NEC to provide the flexibility sponsors may need to evolve their use of DHTs as this area of technology continues to rapidly develop. For example, OSTP and NEC can encourage this flexibility by prioritizing a technology neutral policy to sponsor use of DHTs, and by reinforcing that DHTs may be upgraded mid-investigation if its capabilities and performance initially authorized for the investigation are possible. In other words, sponsors should not be discouraged from leveraging improved features and enhancements to DHTs they are already using in an investigation.
- Development and Use of Novel Clinical Endpoints: DHTs can and should unlock novel clinical endpoints that will provide opportunities for additional insights into participant function or performance that were previously not easily measurable, including and/or in combination with Clinical Outcome Assessments (COAs) and biomarkers, outside of a clinic setting and over time, and that such insights will be crucial to improved clinical investigations. Sponsors should develop and utilize novel clinical endpoints based on input from stakeholders (i.e., patients, disease experts, caregivers, clinicians, engineers, and regulators) to ensure that the novel endpoint is both clinically relevant and the data is adequately captured by the DHT. To augment existing guidance on this topic, CHI has proposes that FDA provide further insights into validation of novel clinical endpoints in the event that such a novel clinical endpoint combines COAs and biomarkers, including whether a sponsor needs to address each component of the combined novel clinical endpoint, or if the entire novel clinical endpoint can be used as a justification.
- Address Adverse Events: With respect to the need to plan and train for handling known adverse events associated with a DHT, CHI has supported the FDA in recommending that sponsors develop best practices to address adverse events using the continual data flows that DHTs provide over time. Such best practices

should account for differentiating between true adverse events and false indications of adverse events, consistent with other FDA guidance and industry standards, and enable maximum flexibility for sponsors to appropriately address adverse events (consistent with our recommended approach to the use of DHTs that may enjoy upgraded functionalities after an investigation launches). We urge OSTP and NEC to align its efforts with this important body of work.

- Address Equity: With respect to the design and operation of clinical trials using DHTs, we urge OSTP and NEC to encourage the consideration of health equity goals through the identification, disclosure, and mitigation of biases while encouraging access to databases and promoting inclusion and diversity. Moreover, decentralized clinical trials increase the opportunity for underrepresented communities to participate.
- Hold Further Consultations with Impacted Stakeholders: Hold publicly-accessible workshops, and make publicly available technical resources and educational materials, on how to embrace the use of new technologies and innovations (including mobile apps and the BYOD model) in clinical trials and investigations, which will help address the reluctance of review boards, clinical sponsors, and investigators to embrace advanced technologies into their processes.

It is crucial that the governance models that lie at the foundation of clinical infrastructure operate in a way that supports sharing relevant data to accelerate digital health technology research and encourages engagement of underrepresented communities. CHI appreciates the opportunity to submit its comments to the FDA and urges its thoughtful consideration of the above input.

Sincerely,

Brian Scarpelli
Senior Global Policy Counsel

Leanna Wade
Policy Associate

Connected Health Initiative
1401 K St NW (Ste 501)
Washington, DC 20005

Decentralized Trials & Research Alliance

Response to Emergency Clinical Trials RFI (#87 FR 64821)
Submitted to White House Office of Science and Technology Policy (OSTP)
Submitted on behalf of the Decentralized Trials & Research Alliance (DTRA)
Submitted January 27 2023

Background

The Office of Science and Technology Policy (OSTP) has issued a Request for Information (RFI) to ensure that coordinated and large-scale clinical trials can be efficiently carried out to address outbreaks of disease and other emergencies.

The Decentralized Trials and Research Alliance (DTRA) is a non-profit collaboration with over 125 member organizations working together to ease the global adoption of decentralized research methods. DTRA members represent bio-pharmaceutical companies, technology and service providers, site networks and research centers, advocacy groups and government agencies.

The DTRA glossary defines a decentralized clinical trial (DCT) as:

> A clinical trial utilizing technology, processes, and/or services that create the opportunity to reduce or eliminate the need for participants to physically visit a traditional research site.

Of note, DCT is an "umbrella term" and inclusive of many models and archetypes including both fully-decentralized as well as hybrid approaches.

Central to decentralized research is the use of decentralized research methods which the DTRA glossary defines as:

> Decentralized research methods include technologies (telehealth, wearables, remote clinical assessments) as well as processes (home health, local labs, local imaging, delivery of investigational drug product) used to create the opportunity to reduce or eliminate the need for participants to physically visit a traditional research site

As the nature of a pandemic requires limiting travel, quarantine, and reducing load at hospitals and medical centers, clinical trials relied extensively on the use of decentralized research methods during the COVID-19 pandemic. This included both

continuity measures for non-COVID clinical trials initiated prior to the pandemic, as well as planned measures for outpatient trials of COVID-related therapeutics and vaccines.

Likewise, utilizing decentralized trials and research has proven to be an important measure supporting ecosystem goals of improving diversity and representation in clinical research. Clinical trial participation brings burden to all, but that burden may disproportionately create access barriers for those from underserved communities which may be mitigated through decentralized methods.

Our nation's hospitals and health systems will remain a cornerstone of responding to a future medical emergency, but these institutions risk being saturated or inaccessible to support research. A national plan for prospective emergency clinical trials meant to also support diversity and inclusion must include the thoughtful use of decentralized research methods.

Listening Session

On January 23 2023 DTRA hosted a Listening Session for the OSTP RFI. This session included members of the DTRA community along with invited guests from OSTP, the Office of the National Coordinator for Health Information Technology (ONC) and other federal agencies participating in this RFI.

A recording of this listening session may be found at: https://bit.ly/DTRA-ONC-RFI

The listening session included three themes with insights from DTRA members including:

1. *How might decentralized research be used to enhance equitable participation in emergency clinical trials?*
    - Otis Johnson, Clario
    - Ryan Brown, Circuit Clinical
    - Tufia Haddad, Mayo Clinic
    - Kendal Whitlock, Walgreens
2. *How might regulatory flexibility help accelerate emergency clinical trials using decentralized methods?*
    - Mo Ali, Medable
    - Mark Brown, IQVIA
    - Rasika Kalamegham, Genentech
    - Josh Rose, CVS
    - Steve Walker, CSL

3. *How might we develop a pilot or demonstration project to use decentralized research for emergency clinical trials in a 6-12 month timeframe?*
    - Hassan Kadhim, BMS
    - Greg Licholai, ICON
    - Jane Myles, Curebase
    - Caroline Redeker, Advanced Clinical
    - John Reites, Thread

1. Utilize Decentralized Research Methods to Enhance Equitable Participation in Emergency Clinical Trials (ECT)

Intentionality will be a key element in any solutions that are used to enhance equitable participation in trial in any setting, including emergencies. This will require some planning and testing, so that data-driven approaches to improving participant inclusivity can be implemented in ECTs.

a. In order to participate in a clinical trial, one must have the means to be present at a research center with high frequency – often requiring time from work and transportation being needed during traditional business hours. In the course of a pandemic this is particularly challenging for those identified as essential workers. It has been reported that Black and Hispanic people are overrepresented in the essential workforce. Decentralized approaches can bring the trial to these individuals.

b. Patients have trusted relationships with providers in their local communities, and including these providers can help build trust in research. This engagement can also include sharing of results, which is often a missing opportunity to build trust. For those healthcare providers in diverse communities that are interested in serving as an investigator, we must help in providing tools and infrastructure. For other providers in the community that are not in a position to serve as an investigator, decentralized methods can help them provide participation with remote investigators (such as seeing the investigator via video). Particular attention should be paid to Federally Qualified Health Centers and the potential to build their competency to support research for both conventional studies as well as in emergency situations.

c. Researchers can not rely on technology access or they risk marginalizing patients impacted by the digital divide, and in many cases researchers must maintain options for provisioning technology or network access. Technology solutions are rarely one-size-fits-all, and must accompany strategic and active engagement, education and empowerment. In addition, research participants tend to prefer tools and systems that are familiar to them. Building ways to access 'the familiar'

into a clinical trial setting will help address clinical trial participation by underrepresented groups.

d. Incorporating input into study design from representative patients may help tackle structural issues impacting diverse participation. Researchers must focus not only on input about science and trial design, but also on how participants would prefer to participate. Patient insight gathering must be conducted prior to an emergency situation to enable these insights to be applied systematically and repeatedly across trials in an emergency (such as to support a master protocol developed prior to the emergency).

e. Trust is a significant barrier, but often patients of color are simply not being invited to participate. Equity in inviting participation can be mitigated with decentralized partners, such as through retail pharmacy and other trusted partners within diverse communities.

f. Incentives must be aligned to supporting the emergency clinical trial, both for participants and for investigators. For participants, that might include ensuring early access to any treatments that are approved based on data in studies which that patient supported. For investigators, that might include access to data for research purposes beyond the emergency trial setting, or a mechanism to ensure that trial participation for their patients elsewhere will not lead to financial loss, and that they will be fairly paid for their time. Structuring incentives so that they are clear, fair and non-coercive is complex and needs to be addressed prior to any emergency setting, with input from ethics committees and institutional review boarfds.

2. Regulatory Flexibility May Accelerate Emergency Clinical Trials Using Decentralized Methods

a. State licensing requirements for healthcare providers impact the for a study investigator to enroll and monitor research participants across state lines. Ambiguity between supporting research and providing care must be addressed, and the role of an investigator for a clinical trial operating under an FDA Investigational New Drug (IND) application should not be constrained by legacy state medical licensure constraints.

b. The language in regulations and policies must shift from a focus upon “the site” and focus instead on the investigator and the participant, thereby providing flexibility around the location of participation. The concept of a site implies a single location from which the individual may participate, rather than embracing

the more flexible and technology-supported new models for connecting the investigator and the participant.

c. Technology must be deployed to support the investigator with access and currency of information to allow oversight, ensuring investigators are effective, efficient and confident.

d. Form FDA 1572 has supported research for years during the time when all visits took place at known and predictable research sites. The limits of this form were uncovered during the pandemic when locations became far more expansive, and it is often viewed as inhibiting progress in research beyond the pandemic. Modernizing the form FDA 1572 will help researchers go farther in meeting patients in the community – in routine trials as well as in emergencies. The focus and intent of trial documentation must remain on data integrity and clarity of oversight.

e. New digital endpoints will help to create more location flexibility, and require proper qualification and validation to ensure reliable measurements regardless if taking place in the clinic, at home, or some place in between. Such measurements cannot be developed on-demand during an emergency, and increasing clarity of expectations with digital endpoint validation will help researcher sponsors to make early investments in novel measurements (such as digital endpoints) that may prove critical in times of emergencies.

f. Continuing support for electronic source data (eSource) will be a critical ingredient to ensuring that investigators have complete data access and confidence in their ability to fulfill their oversight responsibilities. Where data can be collected electronically agnostic to location, appropriate tools can then ensure the investigator has timely data access and control over integrity while supporting patient privacy and data security.

g. With distance increasing between the participant and a research site, studies will grow dependent upon the ability to access trusted electronic health data with a participant's permission which may be obtained during the informed consent process. FHIR-based standards for extracting study data from the electronic health record will support emergency trials with screening, eligibility, safety monitoring, and measuring efficacy. Interoperability – potentially at international scale – will be critical to realize this opportunity, and technology providers must support flexibility and configurability to enable data interoperability. Such interoperability will support transparency and confidence

in data.

h. Proactive policies for permissioned data sharing will improve data gathering in emergency situations, both for individual participants as well as institutions to choose to share data. Data protections as well as access rights must be explicit for participants, as well as researchers. Currently data access limitations will significantly complicate building an emergency trial-ready data aggregation strategy.

3. Opportunities Exist for Pilots or Demonstration Projects Using Decentralized Research for Emergency Clinical Trials in a 6-12 Month Timeframe

a. Pilot/demonstration design considerations:
   i. Demonstrate a simple design that mimics clinical practice to test an ability to engage a diverse population of patients and providers to participate in research.

   ii. Demonstrate the ability to efficiently populate clinical research data from existing electronic health records, such as through repurposing solutions developed to support the National Institutes of Health All of Us program.

   iii. Develop a scoring system to evaluate the readiness of sites and care settings to rapidly deploy decentralized research methods to reach representative patients for potential emergency clinical trials.

   iv. Develop and demonstrate new incentives for community physicians to educate and engage their patients in research participation (such as novel and compliant reimbursement strategies for research screening).

   v. Develop and disseminate templates for business continuity plans to include within clinical trial protocols to provide proactive planning for emergency situations.

   vi. Develop pathways for pre-approval for areas such as with regulators for conducting specific study assessments remotely via telehealth or with institutional review boards for pre-contracting research investigators. Explore an ability to confirm a list of pre-defined assessments and endpoints to support emergency trial readiness; this may including supporting data flow such as FHIR-enabled data extraction from electronic health records to supplement trial-specific data.

vii. Demonstrate the impact on speed, oversight and data integrity with studies using highly centralized approaches for technology and services as compared with those using technology and capabilities available at the site.

b. Pilot/demonstration population considerations:
   i. Consider focusing on first responders (health/medical, police/fire, military) or essential workers as research participants given their significant role and exposure in the event of an emergency. Note that first responder and essential worker roles are often filled with a higher proportion of underrepresented populations.
   ii. Consider demonstrations that may include therapeutic areas or indications that may be difficult to reach in an emergency situation.

Conclusion

The members of the Decentralized Trials & Research Alliance thank the OSTP and their partners for leading on this important issue for ensuring research in times of crisis, and look forward to opportunities for collaboration in the period beyond the RFI.

Prepared by:
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January 27, 2023

Dr. Arati Prabhakar
Director of the Office of Science and Technology Policy
Eisenhower Executive Office Building 725 17th Street NW
Washington, D.C., 20500

Submitted online via emergencyclinicaltrials@ostp.eop.gov

Dear Dr. Prabhakar,

The Infectious Diseases Society of America (IDSA) and the HIV Medicine Association (HIVMA) appreciate the opportunity to provide feedback to the Office of Science and Technology Policy (OSTP) on clinical research infrastructure and emergency clinical trials.

IDSA and HIVMA represent more than 12,000 infectious disease physicians, scientists, public health practitioners and other health care professionals specializing in infectious diseases. IDSA members focus on the investigation, diagnosis, prevention and treatment of infectious diseases, and are involved in both patient care and clinical research. We are pleased to offer recommendations to OSTP that we believe will help strengthen the clinical research infrastructure and increase participation in clinical trial research, including emergency clinical trials.

Governance for emergency clinical trials response

COVID-19 has demonstrated the importance of establishing strong protocols and infrastructure for emergency clinical trials well in advance of an emergency. Federal interagency collaboration is critical to facilitate clinical trials in emergency situations. **To achieve this, it's important to develop formal collaborations and partnerships between agencies, including OSTP, the Food and Drug Administration (FDA), the National Institutes of Health (NIH), the Centers for Disease Control and Prevention (CDC), the Agency for Healthcare Research and Quality (AHRQ), the clinical research community and the health care provider community to strengthen and improve the clinical trial infrastructure, expand funding mechanisms and develop better analytical and predictive tools**. Additional federal efforts should re-evaluate the US Food and Drug Administration's emergency use authorization process for therapeutics and the interplay between expanding access prior to drug approval with the need for sufficient clinical trial data from a diverse patient population to support approval. IDSA and HIVMA recommend adopting policies that align with those applied to the COVID-19 vaccine authorization and approval process, such as publicly communicating data for EUA and for

subsequent approval in addition to publicly releasing clinical data before authorization and prior to subsequent approval.

IDSA and HIVMA recommend that the FDA:

- Establish and publicly communicate benchmarks for vaccines, diagnostics and therapeutics for pathogens causing an emergency to receive an EUA, as the agency did for COVID-19 vaccines, and requirements for receiving licensure after an EUA is granted
- Require the public release of clinical trial data both before a therapy receives an EUA and before it receives subsequent routine approval
- Require the sponsor to have a plan for completing and publishing data from definitive clinical trials post-EUA and to articulate a plan for pursuing approval or licensure once granted an EUA.
- Require the sponsor to include plans for recruiting children, individuals who are pregnant and breastfeeding, and individuals who are immunocompromised, including people with HIV, in addition to populations who are typically disproportionately impacted by infectious diseases and emergencies, including Black, Indigenous and other people of color, Latinx communities and other underserved populations.
- For products available through an EUA, collaborate with manufacturers, health care facilities, private and federal payers and other federal agencies to collect additional evidence to monitor safety and efficacy.

Federally supported infrastructure should provide an integrated framework to link individuals diagnosed with emerging infectious diseases to appropriate trials and encourage large-scale collaboration across many different types of facilities, including community hospitals and community health centers. Such an approach will increase the reach of trials of promising therapeutics to populations that are typically underrepresented in studies, including African American/Black, Latinx and Indigenous populations, children and adolescents, and adults aged 75 and older. This goal is best accomplished by performing studies on larger, more diverse populations, with a focus on settings outside the traditional urban tertiary care academic centers. Increasing access to clinical trials in rural areas should also be considered through this approach. These considerations increase access to treatments for patients and the ability to gather data across a broader range of participants more rapidly.

In addition to clear communication across federal agencies, communication with the clinical research community should remain a priority. When communicating the decision to begin emergency clinical research, institutions should receive clear, unified guidance from the federal government that outlines next steps in carrying out emergency clinical trial research.

Additionally, the federal government should support the expansion of pragmatic trials networks (e.g., FDA Reagan Udall COVID-19 Diagnostics Evidence Accelerator, Sentinel, PCORnet, NIH Collaboratory), including networks that enroll pediatric populations, to

rapidly generate real world data and inform the development of therapies and diagnostics in the case of a public health emergency (PHE). In the development of these trials, federal agencies should increase efforts to engage frontline physicians and community clinicians in clinical trial research and development, especially in ongoing clinical trial infrastructure. Specifically, the federal government should involve from trial inception clinicians, researchers and community members representing the population being studied or who have lived experience of the health issue. Frontline physicians and other community clinicians can offer insight to trial planning. As active members and trusted figures in trial site communities, these individuals help build transparency and public trust in addition to improving clinical trial design. Additionally, they help expand potential trial participant pools, which can improve trial diversity. **Studies have shown that involving clinical researchers can ease the translation of research results into clinical care.** We also can learn from the success of the United Kingdom and other countries in setting up rapid pragmatic trials during the COVID-19 pandemic.

Designating funding in federally funded clinical trials to support training and logistical support for community and frontline physicians can incentivize involvement from these groups. When developing emergency trials in response to emerging infectious diseases, it is also crucial to involve ID physicians working in healthcare settings when possible, as well as pediatric ID physicians to better engage pediatric populations.

A successful effort to build clinical trials infrastructure for public health emergencies must be coupled with an effort to strengthen the infectious diseases (ID) workforce, including ID physicians and ID physician-scientists, who are often called upon to lead clinical trials and enroll patients, as we saw during COVID-19 and mpox. Unfortunately, the ID workforce is struggling to recruit, as only 56% of ID fellowship training programs filled their slots in 2022. Persistent recruitment challenges and workforce shortages are due in part to financial issues. ID is one of the lowest paid medical specialties, and high medical student debt is a key factor that drives many to higher paid specialties. IDSA and HIVMA recommend:

- Improve reimbursement for non-procedural care.
- Establish a new mechanism to ensure that clinicians are able to be reimbursed for additional work performed during an emergency, including clinical trial enrollment.
- Fund and implement the new BIO Preparedness Workforce Pilot Program to provide loan repayment for ID clinicians working in underserved areas.
- Increase NIAID funding and strengthen NIAID policies to support early career investigators, mentorship and transitions from training to faculty, and opportunities for community-based physicians to participate in clinical research.
- Additional recommendations to strengthen the ID physician-scientist workforce are available here.

Identifying and incentivizing research institutions and networks; building diversity and equity

Diversity, equity, inclusion and accessibility (DEIA) should be at the forefront of considerations in clinical trial design at the federal level. **Especially during a PHE, it is critical that medical**

countermeasures and clinical guidance are tailored to diverse populations, for example, considering differences in age, sex assigned at birth, gender identity, ability, racial and ethnic identity and sexual orientation. In funding and designing clinical trials, research should prioritize including diverse participants from a variety of ethnic, racial, gender identity, socioeconomic, geographic and age backgrounds to improve representation in clinical research. African American/Black, Latinx and Indigenous populations and adults aged 75 and older often have markedly low participation in clinical trials, which contributes to health inequities and skewed data and limits applicability of research findings. This imbalance in clinical research inclusion also leads to limitations in applying clinical data to treatment options. Additionally, it is important to increase inclusion of key populations at higher risk for serious illness, such as pregnant and immunocompromised people in clinical research trials, especially in vaccine trials.

To address the lack of diversity and equity in clinical trials, it is important to fund research that looks for the root causes of the issue. **Federal agencies should prioritize and support studies focusing on critical areas in clinical trial research, including research on the effectiveness of recruitment strategies for clinical trial volunteers, factors and barriers that may prevent these strategies from reaching underrepresented populations and the effectiveness of incentives used in clinical trial recruitment, such as paying participants who sign up or reimbursing the time spent on clinical trial activities.** Research into these areas can strengthen and improve the overall effectiveness of clinical trial infrastructure and DEIA efforts.

To increase diversity and equity in clinical trials, it is also essential to develop, strengthen and sustain relationships with underrepresented communities through increased outreach. **This can be accomplished through research teams developing and sustaining partnerships with community-based organizations that have established trust in underrepresented communities**. These collaborations also are also critical to increase participation from underrepresented populations. Sustained work with community groups will require additional funding and long-term investments in research. Community partnerships are important to increase the visibility of research in underrepresented communities, support research literacy and aid in outreach and recruitment of clinical trial participants.

Faith based organizations and institutions in these communities can also be effective partners in disseminating and communicating information to diverse populations and facilitating outreach for clinical trials recruitment in underrepresented communities. When working with underrepresented communities in clinical trials, communication is critical to consider. A recent study in Trials identified that language and communication remain two of the largest barriers to clinical trial participation. Requiring clinical trial research leaders to draft strategies for investigators and researchers to communicate with community leaders to spread information about the trial can help increase participation. Communication strategies should be transparent, and focus on trial procedure, importance of trial participation and impacts and side effects when applicable. Transparency in these communications builds trust with the community and the populations researchers seek to work with. Any communication materials used in trials should be written at an appropriate reading level and available in multiple languages, particularly those commonly spoken in affected communities. All written materials used in the study, especially consent forms, should also be available in multiple languages to encourage

accessibility for participants. Additionally, ensuring translators are readily available for participants is important to increase inclusion and demonstrate a respect for participants and stronger cultural competency in clinical trial design.

Diversity in clinical trial staff is also critical. Research from Tufts found that clinical trial sites with higher racial and ethnic diversity among staff members saw higher enrollment of patients from minority groups. These sites were also more likely to report that they viewed diversity as a critical part of operating procedures and research success. This prioritization of diversity can support more favorable views of researchers and trials by the communities that researchers seek to work with and is critical in furthering DEIA in clinical trial research.

Trial design should address and mitigate barriers for patients from underrepresented groups to participate. For instance, distance to the clinical trial site and travel cost is often a limitation. To address this barrier, clinical trial design should prioritize carrying out trials and procedures at facilities in areas easily accessible to underrepresented populations. Providing transport or ensuring trial locations are near public transit locations can alleviate transport concerns.

Telehealth and mobile vans also should be fully leveraged to extend clinical trial participation to rural communities and to urban health care deserts with limited or no clinical or clinical trial sites.

Additionally, co-locating sites that can perform rapid diagnostic testing with treatment sites, especially in clinical trials occurring during public health emergencies, can facilitate enrollment into clinical trials. This solution reduces inequities related to access (such as transportation) that occur when testing and treatment are separated. Working within the community can also alleviate participant concerns about accessing trial sites. Identifying local clinics and medical centers that can partner with the government or with academic medical centers carrying out clinical trials can greatly increase the proportion of participants from underrepresented groups.

Beyond the incentives identified in the RFI, introducing referral bonuses to trial participants who recruit new participants would be beneficial in increasing overall participation. Other ways to increase participation could include connecting research sites with childcare options, providing opportunities to participate in clinical trials on weekends and/or evenings after 5 PM and compensating participants for travel expenses.

“Warm base” research

Maintaining a “warm base” for clinical trials can help strengthen overall efforts at participant engagement and provide infrastructure. The NIH supported AIDS Clinical Trials Group, HIV Vaccines Trials Network and ACTIV clinical trials demonstrated during the COVID-19 pandemic and the mpox outbreak the value and importance of maintaining clinical trial infrastructure, including researchers and scientists, that can quickly pivot as new infectious diseases threats emerge. Supporting well established clinical trial networks that can be mobilized quickly in the event of a PHE is critical to effective research. Studies show that the mobilization of these existing networks allowed cross-study comparisons that dramatically increased the

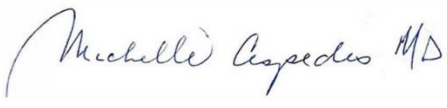
speed of review and approvals of COVID-19 vaccinations. However, these efforts should be in place well before emergency trials are necessary. W**arm base research partnerships with communities over long periods of time, as exemplified with HIV research mobilized for COVID-19 trials, builds on established trust with patient groups, and can increase overall inclusion of patients from diverse backgrounds in emergency clinical trials.**

Additionally, federal efforts can leverage private-public partnerships with relevant stakeholders to ensure sustained funding and resources to maintain "warm bases" for clinical trials. **These models should engage diverse, underrepresented populations and utilize community engagement strategies similar to those listed above. Engaging community and frontline clinicians in these efforts can help maintain these "warm bases" through active community outreach.**

"Warm base" research can be incredibly useful in infectious diseases clinical trials. **Emerging infectious diseases threats require infrastructure and patient populations that can be rapidly leveraged to develop an understanding of a possible unknown pathogen and methods to prevent and treat it**. Funding "warm base" research on existing infectious diseases creates this infrastructure. For example, studies have outlined how the US National Institute of Allergy and Infectious Diseases (NIAID) supported collaborative government to government research in countries like Mexico and Indonesia that focused on different infectious diseases such as acute febrile illness and respiratory diseases. When COVID cases surged in 2020, these clinical trial studies were able to be rapidly repurposed to COVID testing and study. Similar efforts in the US can leverage research on endemic infectious diseases, and then be rapidly repurposed to study future emerging infectious diseases. Ongoing research and clinical trials on infectious diseases such as COVID-19 or influenza can then be utilized to rapidly study and conduct emergency clinical trials for emerging respiratory viruses.

IDSA appreciates the opportunity to comment on improving clinical trial infrastructure and emergency clinical trials. If you have questions about these comments or would like to connect, please contact Eli Briggs, Director of Public Policy, at ebriggs@idsociety.org or Andrea Weddle, Executive Director of the HIV Medicine Association, at aweddle@hivma.org.

Sincerely,



Carlos Del Rio, MD, FIDSA

President, IDSA

Michelle Cespedes, MD, MS

Chair, HIV Medicine Association

January 27, 2023

Submitted electronically to emergencyclinicaltrials@ostp.eop.gov

Ms. Grail Sipes
Assistant Director for Biomedical Regulatory Policy
Office of Science and Technology Policy
Executive Office of the President
Eisenhower Executive Office Building
1650 Pennsylvania Avenue
Washington, D.C. 20504

Re: Request for Information on Clinical Research Infrastructure and Emergency Clinical Trials

Dear Assistant Director Sipes:

The Alliance for Connected Care ("the Alliance") welcomes the opportunity to provide comments on the White House Office of Science and Technology Policy (OSTP) request for information on clinical research infrastructure and emergency clinical trials.

The Alliance is dedicated to improving access to care through the reduction of policy, legal and regulatory barriers to the adoption of telemedicine and remote patient monitoring. Our members are leading health care and technology companies from across the spectrum, representing health systems, health payers, and technology innovators. The Alliance works in partnership with an Advisory Board of more than 40 patient and provider groups, including many types of clinician specialty and patient advocacy groups who wish to better utilize the opportunities created by telehealth.

As reflected in the comments below, utilization of telehealth proliferated throughout the pandemic and has significantly improved access to care, care coordination, patient engagement, and more. Telehealth and remote patient monitoring are important tools that can be leveraged in clinical trials to bring innovative services and treatments to those with the least access to it, however there continue to be barriers in place that impede such access. In our comments, we outline licensure restrictions that present a barrier to clinical trial recruitment and diversity and present a recommendation for OSTP's consideration.

Effective ways to increase diversity among study participants and investigators, and to expand clinical research sites into underserved areas

Digital technology is giving health care professionals new tools to deliver care to patients in addition to giving patients new access to care. The pandemic demonstrated that digital care can build capacity for care in rural and underserved areas, and areas experiencing provider shortages. Provider shortages are associated with delayed health care usage, reduced continuity of care,

higher health care costs, worse prognoses, less adherence to care plans, and increased travel. In addition to being a tool to address such barriers, telehealth services play an important role in supplementing and strengthening clinician networks available to patients. Telehealth can be leveraged to strengthen the delivery system by providing highly specialized services in areas where clinicians with these skills are not available to consumers.

As one goal of this emergency clinical trials initiative is to support the expansion of clinical research into underserved communities, and increase diversity among both trial participants and clinical trial investigators, the Alliance believes that continuing to modernize and decentralize clinical trials is critical for creating opportunities for more diversity and patient engagement.

Obviating the need for travel time, lost wages and childcare/eldercare through use of digital technologies will significantly increase the pool of potential participants in clinical trials across geographies. Decentralizing clinical trials is also critical with respect to advancing health equity by accounting for such logistical and other participant-related factors that could limit participation, and would also help improve recruitment, retention, and participation in clinical trials.

One barrier in using digital technology in clinical trials is the state licensing limitations that effectively prohibit clinicians working on clinical trials from recruiting patients from outside the state where the clinician is licensed, thereby creating a barrier to entry for use of decentralized trials and diminishing the impact of federal changes aimed at decentralizing clinical trials. This is especially important for rare diseases affecting fewer than 200,000 people in the United States, for which utilizing clinical trials across state lines may significantly increase the likelihood of a successful and diverse clinical trial.

To address this issue, the Administration could direct the U.S. Food and Drug Administration (FDA) to provide non-binding guidance to states on how to bolster clinical trial modernization through licensure flexibilities to help catalyze change at the state level. We recommend that the FDA set up an intergovernmental working group with state and federal regulators to develop such guidance. This group will likely identify other areas beyond licensing that may need to be addressed, such as mailing of non-approved medications.

We are hopeful that OSTP would agree it is important to promote harmonization between state and federal regulators within the United States. We see efforts to mitigate state licensing limitations as one way the Administration can act to address the barriers in decentralizing clinical trials to increase their success and participation.

***

Thank you for the opportunity to provide comments on this important issue. We hope you will consider this recommendation as you examine ways to increase access to clinical trials through digital technologies and see the value of telehealth in providing greater access to clinical trial participation.

We look forward to working with you and welcome further discussion on this topic. Please reach out to Casey Osgood Landry at casey.osgood@connectwithcare.org with any questions.

Sincerely,

Executive Director
Alliance for Connected Care

Request for Information; Clinical Research Infrastructure and Emergency Clinical Trials

Responses provided by Curebase, Inc.
Jane Myles, MSc Pharmacology/ Toxicology - VP Clinical Trial Innovation
Laura Podolsky, JD, MPH - General Counsel

Identifying and Incentivizing Research Institutions and Networks; Building Diversity and Equity

a. *Methods for identifying institutions and sites that may have an existing interest in or familiarity with emergency clinical trial research. This might include those that currently receive government funding, those with a focus on infectious disease research, and/or those that have worked with CROs.*

Identifying institutions and research physicians for clinical studies is best conducted in preparation for an emergency clinical trial (ECT), not in an active crisis. During the pandemic, it became common to identify, train, and support de-novo research sites to participate in clinical trials. While some companies harnessed their existing site networks to execute trials at scale, Curebase saw success by working individually with physicians and supporting their path to research readiness. This was accomplished by providing training, CRC support, decentralized clinical trial tools, an eClinical platform, and other resources required to participate in clinical studies. We recommend identifying these physicians by providing clinical trial training and protocol awareness tools during traditional physician training (specialist fellowships, final GP practicum training, etc.). Physicians could also benefit from consolidated communication informing them of open trials - this could be accomplished by using standard healthcare tools such as EMR or institutional communication platforms.

b. *Effective ways to increase diversity among study participants and investigators, and to expand clinical research sites into underserved areas. It would be helpful to get input on whether and how the following approaches would be useful:*
   i. *Community outreach.*

The general public lacks understanding regarding the connections between clinical trials, research, public health, and the successful implementation of new treatments. To bridge this gap, we suggest beginning with a community education program focused on participants, their local physicians, and influential community groups. Such a program should use simple, culturally sensitive content that explains the individual benefits of clinical research for patients, physicians, and the larger community. The materials need to be similar and connected, with messaging appropriately adjusted for the audience. The Center for Information and Study on Clinical Research (CISCRP) could be considered a

subject matter expert in developing these materials and delivering them to the community via well-established programs like The Medical Heroes and Aware for All.

Such a community outreach initiative (e.g. materials, messaging, community events) can leverage the infrastructure that is already in place, such as:

- The clinical trial infrastructure being built at retail pharmacies (e.g. Walgreens and CVS)
- Urgent care centers and community clinics where under-represented participants often seek medical care
- Screening programs for general well-being, such as heart health, COVID diagnostics clinics, or patient care centers (e.g. Quest Diagnostics or LabCorp)

Simultaneously, a call-to-action campaign directed toward physicians in underserved areas could explain the value of participating in clinical trials, the opportunities that clinical trials present to impact their patients' health, and the financial considerations posed by public health emergencies (both potential financial incentives and broader impacts). The content for such a program would be connected to that created for participants to generate a consistent, unified message. This could be communicated through already-existing platforms used by physicians within their healthcare systems (e.g. EMR system-wide content) and physician-to-physician networks (e.g. Doximity, Sermo, etc.)

ii. *Use of decentralized clinical trial (DCT) design elements, or other innovative approaches such as trials conducted at the point of care.*

Decentralized clinical trial (DCT) design elements reduce many of the barriers to entry that potential participants face when considering enrolling in clinical trials. Travel time, associated expenses, geographic location, and indication severity are all factors that can exclude or dissuade participation in research trials but can be mitigated by the use of DCT technologies. Trials that are able to recruit outside of urban areas can engage under-represented members of the population, potentially increasing the diversity and accessibility of studies. The use of DCT methods increased rapidly during the pandemic because they were an effective way to minimize in-person contact while studying and treating a highly infectious disease. This decreased the risk of participation in trials, particularly among the elderly and immuno-compromised, safely expanding the reach of studies to those who were most vulnerable.

While some DCT design elements were utilized extensively during COVID-19 lockdowns, there is an opportunity to increase the use of individual tools (e.g. eConsent) and standardize these methods as part of standard clinical trial execution. For example,

while telehealth was adopted broadly to ensure trials could continue during COVID-19, too few trials continue to offer telehealth visits as a standard option outside the circumstances of a public health emergency. The same is true of eConsent, in-home visits with nurses and phlebotomists, and even eCOA for capturing patient-reported outcomes.

There are many different platforms that already offer these DCT elements. Ideally, clinicians interested in contributing to ECTs would be proactively trained on such tools, increasing their willingness to participate in ECTs while decreasing risks to data quality. This could be accomplished through the "warm base" pilot program by integrating training for DCT elements across simple-to-use platforms prior to the activation of an ECT. A key component of this effort will be designing research protocols that optimize the use of DCT elements: it is much simpler to write a protocol with the intent of utilizing DCT elements as opposed to retroactively fitting DCT tools to a protocol intended for brick-and-mortar research. This way, DCT eClinical platforms and technology-driven services are built into the training and promotional materials for the ECT, allowing investigators and patients to learn about the research experience in a simple, modern, and cohesive way.

iii. *Use of technological innovations, such as digital health technologies (DHTs), that would allow remote participation or otherwise limit the need for participants to travel.*

DHTs (digital health platforms, wearable sensors, telehealth, etc.), if properly validated and implemented, have significant potential to bolster the accessibility, ease, and accuracy of ECTs and promote the democratization of healthcare. DHTs and DCTs go hand-in-hand: both allow clinical trials to move out of the traditional research setting and into patients' homes. This may significantly reduce common barriers to entry such as geographic location, travel constraints, financial constraints, and time commitment. DHTs can also lend themselves to higher data quality due to the virtually unlimited number of data points that may be collected over time and the authenticity of the testing circumstances - traditional clinical trials are limited to only the data points collected when patients are in the clinic. Furthermore, DHTs provide the opportunity to share data back to participants. Current clinical trial standards largely leave participant data in the hands of the investigators, with little to no feedback for participants unless the study is intended to inform treatment decisions. Returning data to participants could have a number of benefits, including incentivizing participation, increasing transparency in clinical trials, and even potentially sharing anonymized insights across studies.

However, while such technologies are making inroads into clinical research, they are not yet a standard; investigators, sponsors, and participants are not yet widely familiar with

these tools. They have different needs than traditional data sources regarding data collection, monitoring, and logistics, particularly at scale. DHTs are also difficult to implement retroactively - studies that want to incorporate DHTs are most successful when the protocol is written for those technologies.

In addition to DHTs, an increasing number of in-home biospecimen self-collection products are becoming available for use in both clinical practice and clinical trials. Integrating solutions like these could significantly decrease the need for patients to travel to have biospecimens collected. Naturally, sponsors and regulators will want evidence that these solutions meet data quality and patient adherence expectations. We recommend incorporating self-collection solutions into a "warm base" research pilot to support that evidence generation.

iv. *Building on existing programs that target diversity in clinical research, including initiatives within research institutions and public-private collaborations.*

We recommend leveraging key learnings from the NIH All of Us research project to understand how to overcome barriers to access as well as how to work within communities that do not typically participate in clinical trials. The All of Us project has developed key practices to work with these communities, using culturally sensitive approaches to start building trust and generating participation from members within them. In particular, the work done to partner with American Indian/Alaska Native (AI/AN) tribal councils would be useful to understand and adapt for a future ECT setting.

If a "warm base" project goes forward, we recommend that a framework for diverse clinical trial participation is developed aligning with the FDA's document "Diversity Plans to Improve Enrollment of Participants From Underrepresented Racial and Ethnic Populations in Clinical Trials." This would help build familiarity with implementing any new practices in a non-emergent setting, which ideally could be adapted in the future for ECT situations. While this seems intuitive, if we anticipate a recurrence of clinical trial-naive sites participating in the next ECT it is critical to support these sites on the mission of clinical trial access equity. This includes the practical implementation of recruitment and engagement tactics to create awareness within and ease the hesitancy of underrepresented populations to participate in clinical trials.

v. *Leveraging the networks and community access of retail chains, including retail pharmacy chains*.

Retail chains, especially pharmacy chains, can be an essential part of any ECT solution in the US. These entities have deep roots in all communities, including underserved

communities and underrepresented populations. These relationships can support the awareness and trust-building that will be essential to enroll participants in trials. Over time, these parts of the ECT network could become an important way to seek patient input into trial design and execution strategy. In the shorter term, they offer a place to systematically ask people what they need to join a trial and what barriers individuals in these communities are facing that are precluding them from being trial participants.

c. *Incentives that can be identified or enhanced to encourage participation in emergency clinical trial research.*
   i. *As described above and in the forthcoming RFI on data capture for Emergency Clinical Trials and Data Collection Pilot, we are seeking information on how to create a pilot program enabling clinical trial data collection across a wide variety of trial sites that is easy for health care providers to use and can be scaled up for use in emergency research settings. It would be helpful to receive comments on whether the opportunity to participate in such a pilot program could create an incentive for institutions and sites to participate in emergency clinical research studies.*

Physicians don't typically participate in clinical research, and a large portion of those who become investigators do so for only one trial. To create ECT ready-sites, we need to reduce the complexity of the trial design and data collection. This could be accomplished by fitting the trial as closely as possible to existing standards of care: building the protocol to align with clinical care, using the standard associated data, and extracting said data from electronic health records (EHR). Such an approach helps to ensure that the trial participant stays in the care of their treating physicians and alleviates the physicians' concerns that they will lose patients from their practices. Demonstrating that patients don't leave the practice could be an important incentive for physician participation in ECTs.

Additionally, we recommend planning the trial design to leverage Real-World Data (RWD), limiting the repetition of clinical assessments that are standard of care and improving the cross-ecosystem experience between clinical care and clinical trials. The incentive structure for RWD is intrinsic; it reinforces data quality and completeness and supports decision-making based on trial results.

It may also be useful to harness existing healthcare networks and provide incentives to members to become trained research investigators. Networks of physicians seeking qualified health information network (QHIN) status are particularly promising. If a given network has a base of practicing physicians, it may be reasonable to set a target for a percentage of those physicians to become "clinical research-ready." This could be achieved through training, contractual agreements, and the completion of the regulatory

documentation required for trial participation. Incentivizing this process would align the objectives of the healthcare networks, the physicians who wish to offer their patients innovative treatment options, and the ONC/OSTP.

d. *Once interested institutions or networks are identified*

ii. *Information that should be collected from interested sites, for example by means of a short questionnaire to assess characteristics of patient population, level of training that would be required, etc.*

Interested sites could submit de-identified datasets that capture the broad parameters of their patient population. These could be used to evaluate the candidacy of individual sites for specific trials - for example, those with a high proportion of patients with a specific indication, age range, or treatment regimen. We recommend establishing common parameters and centralizing the analysis of said data to ease the administrative burden on the sites themselves. This will also serve to establish direct comparisons between research sites to aid in the identification of best-fit sites in an ECT situation. The rapid activation of those sites would depend on a clear and coordinated outreach plan, ideally using communication channels that are already standard use at sites (e.g. EHR messaging tools).

e. *The best ways to provide training in clinical trial practice (including regulatory requirements such as Good Clinical Practice (GCP)) where needed, targeted as appropriate to staffs' roles, including staff at sites that may not have participated in clinical trials previously.*

We recommend leveraging an available GCP/clinical research readiness solution. Several organizations offer these training sessions both for independent study and remote or in-person classes. For example, the NIH offers GCP training modules that are free of charge for any user. To reduce the administrative burden on sites, we advise establishing common standards for GCP training and providing resources to programs that meet those standards.

Curebase routinely identifies and trains research-naive investigators, and has found success in using standard technology and training materials distributed through our DCT platform. We have observed improvements in the speed of recruitment, diversity of recruited participants, geographic reach of studies, and data quality with this approach. Several other DCT organizations have created similar solutions, and there is a growing familiarity with such processes amongst the clinical trial community. Another potential solution could be to partner with integrated research organizations (IROs) that actively identify, train, and support new research sites, broadening the pool of clinical research

investigators. Examples of such IROs include Javara and Circuit Clinical. There is an opportunity to iterate on their materials and operating models to create "research-ready" sites in underserved areas of the US.

"Warm Base" Research

a. *Disease areas that should be targeted in protocols for "warm base" clinical research. It would be helpful to get comments on:*

   i. *Disease areas that are most relevant to communities, including underserved communities and those that may have little experience with participating in clinical research.*

We recommend that the initial "warm base" research align with well-understood and highly prevalent disease areas. Infectious diseases (IDs) are a strong target - they affect many communities due to the nature of their spread, nearly everyone can participate (patients with the target indication and healthy volunteers), and they are the most likely cause for the next ECT scenario.

If there is interest in creating a real-world data (RWD) or registry trial system, heart disease and/or diabetes are a strong fit. These indications have a high incidence and impact among underrepresented populations. There are educational materials and programs already in place from the CDC and NIH regarding the treatment and prevention of heart disease; these could easily become part of an awareness campaign to participate in pilot research programs.

   ii. *The extent to which "warm base" research should target infectious disease, versus other conditions such as cancer, heart disease, or rare disease; and the size or scope of site networks that would be needed to study various conditions.*

A "warm base" focused on IDs would allow the suggested clinical trial network to act as a pilot for the next emergency - the associated solutions, protocols, containment measures, diagnostics, data, and communication would all be practiced and iterated upon to make the most successful emergency response. One such indication that could fit well into this scenario is the flu and its associated annual vaccine. Beyond creating a systematic response for the next public health crisis, this "warm base" can meet existing research needs by creating a collaborative network for testing new diagnostics and updated flu vaccine strains, effectively creating a more cohesive database of patient outcomes. These research initiatives are closely aligned with the trials that were required to respond to the COVID-19 pandemic - a testament to the advantage of targeting IDs in "warm base" clinical research.

As mentioned above, RWD/registry trials on heart disease and/or diabetes could reach underrepresented populations and provide a large pool of community-based physicians and patients. This would allow the opportunity for GCP training and research readiness preparation without any regulatory risk. In turn, allowing an option for the stakeholders in this group to opt into future ECTs and research initiatives would create a large "research-ready" pool of investigators and patients.

b. *How "warm base" research could best be implemented to provide training to sites that are inexperienced with clinical trial research, and to create a basic level of surge capacity at the staff level for emergency clinical trial research. We would appreciate input on other training mechanisms that could be used here as well.*

Many platform solutions exist today for the distribution and management of clinical training. We recommend allowing several such platforms to be used, contingent upon their alignment on content and testing criteria, because it would likely reduce the tech burden and subsequent resistance to adoption by research-naive sites. Since most clinical sites already require training on patient care and confidentiality, adding modules to their existing training system would greatly simplify their entrance into the proposed ECT network. Another way to ease access to participation in "warm base" research would be to consolidate messaging and training for new sites via deployment through the existing EHR system. Overall, integrating the required training and communication into the systems and processes that are already in use will likely be the most successful implementation strategy. Additionally, as previously described, IROs may be well-suited to help with the recruitment and training of de-novo research investigators and can offer valuable insight into the successful identification and training of new research sites.

The "warm base" pilot itself can be used as a means to test the ease of use and effectiveness of research readiness training including GCP requirements, regulatory documentation standards, IRB interaction, and trial oversight expectations. It will provide a foundation upon which the ECT network will be able to iterate, eventually ensuring a systematic process that can bring research-naive sites into clinical trials with ease and success.

c. *Whether "warm base" research could be appropriately supported as*
   i. *A demonstration project with commercial partnership*

Yes - for example, an RWD commercial entity or data tokenization organization could support a prospective registry trial.

   ii. *A public-private partnership*

Yes - for example, drug development and diagnostics-focused companies could create a pilot to solve a scientific problem together while simultaneously building the "warm base" research network. This would require some careful prospective thinking on data use, data ownership, and how the data would be used to meet the goals of the respective companies and the ECT program. This would also allow the opportunity to align on key endpoints, data variables, and primary objectives - potentially creating the backbone of an eClinical platform protocol for use in the prospective ECT setting.

iii. *An agency-funded program*

This may be the most practical approach, assuming sufficient funding is available. The biggest challenge with this approach is driving progress quickly enough to ensure that a "warm base" pilot can be executed with enough simplicity and rigor in a timely fashion.

Emergency Master Agreement

a. *Basic terms that might form part of an Emergency Master Agreement, including the following:*

i. *Data collection and use, including ownership of the study data and biospecimens; entities that have the right to collect, store, and use the data and specimens; banking of biospecimens for further research*

We would suggest using a template agreement that many institutions are already familiar with, like the Accelerated Clinical Trials Agreement. Keeping the terms as simple as possible can help reduce negotiation time. If possible, the project could make data accessible across the ECT ecosystem and include sharing data back to individual research participants for their own health records.

ii. *Use of a single IRB across all participating trial sites. As a related point, it would be helpful to get feedback on whether an IRB should be established that is primarily devoted to emergency clinical trials.*

We recommend using a central IRB to facilitate trial review, responses to questions, approvals of the original and amended protocols, and consent forms. This will simplify the process across the entire ECT network of sites and research entities. We strongly advise testing this approach in a "warm base" pilot to understand the feasibility of such a process and to discover any unanticipated complexities involved in executing the research.

We also advise against creating a specific entity to support ECTs unless there is evidence that the current central IRBs would not have the capacity to manage the suggested workload. If the ECT program is successful, ideally fewer, larger trials would be submitted for review and approval by IRBs.

Utilizing OneSource to Enable Overnight Implementation of Clinical Trial Data Capture for Public Health Emergencies

Prepared by:

Quantum Leap Healthcare Collaborative

OpenClinica, LLC

In response to:

RFI: Clinical Research Infrastructure and Emergency Clinical Trials

FR Doc. 2022–23110

Note to reader:

A technical description of OneSource and a description of current gaps in eSource development and implementation is provided in the authors' response to "Request for Information on Data Collection for Emergency Clinical Trials and Interoperability Pilot," FR Doc. 2022–23489.

Executive Summary

Data capture, cleaning and validation in clinical trials entails a significant investment in terms of time and resources, and the need for source data verification (SDV) causes delays in the availability of quality data. Furthermore, the lack of interoperability in health data systems and the complex nature of the datasets impedes the sharing and reuse of data across multiple nodes. In detecting and in response to public health emergencies, the timely availability of quality data is paramount, as is the ability to share and analyze data pooled from multiple clinical sites and in the context of the current state-of-the-art in relevant therapeutics.

The OneSource platform, developed by Quantum Leap Healthcare Collaborative and OpenClinica in collaboration with the FDA, streamlines the capture and reuse of clinical and research data at the point-of-care. OneSource is the only integrated electronic health record (EHR)/electronic data capture (EDC) solution that captures regulatory-grade data from Epic and Cerner EHRs with both Clinical Research Coordinator (CRC) and patient-mediated data access. The platform includes best-in-class solutions for electronic data capture (EDC), electronic patient reported outcomes (ePRO), biospecimen, trial randomization, safety reporting and site payment systems that are fully integrated.

OneSource is designed to work in tandem with US Core Data Interoperability (USCDI) standards to permit structured data capture directly from the EHR for reuse in clinical trials, registries or other secondary uses.

By establishing the capture of USCDI data elements as a standard part of clinical care between public health emergencies, OneSource would enable overnight, seamless transition to the automated capture of regulatory grade data for clinical trials, including patient characteristics, diagnostics and diagnoses, laboratory measures and outcomes, at all clinical sites. Direct capture from the EHR without human intervention significantly reduces human and financial resources required for data capture, while vastly increasing data fidelity and reducing the need for source data verification. This means faster access to better quality, highly portable data. Furthermore, in times where no emergency exists, OneSource can facilitate the creation of low-cost, low-maintenance registries that can be used for monitoring/surveillance purposes, to detect outbreaks on a national or local scale, and establish baseline outcomes that may provide important guidance on potentially effective treatment strategies early in the response to the emergency.

About the Contributors

Quantum Leap Healthcare Collaborative

Quantum Leap Healthcare Collaborative (QLHC) is a 501(c)(3) charitable foundation supporting the development and implementation of innovative ways to deliver better, less costly healthcare. QLHC has successfully established unique partnerships across the medical, technology and bioscience industries, as well as the federal government, all necessary components to accelerate healthcare research into the marketplace. QLHC's efforts focus on quality-of-care and quality-of-life issues and creating initiatives that foster excellent clinical practices using quality improvement disciplines with a strong patient-centric focus. QLHC is the sponsor of the I-SPY family of trials: I-SPY2 TRIAL, DCIS RECAST, I-SPY COVID Trial and I-SPY Phase 1b. The I-SPY2 TRIAL (Investigation of Serial studies to Predict Your Therapeutic Response with Imaging and Molecular analysis) is the longest running platform trial, continuing its operations for over 10 years. QLHC has extensive experience building and managing coordinating centers and executive steering committees for scientific direction and program governance. There are approximately 40 trial sites in the QLHC network including many major academic centers and major healthcare providers.

www.quantumleaphealth.org

OpenClinica

OpenClinica was founded in 2006 as an Open Source Electronic Data Capture (EDC) platform. In 2017, OpenClinica 4 (OC 4) was introduced, a cloud-based, modern EDC along with modules supporting reporting, ePRO, Randomization, and DICOM integration. Starting in 2018, we partnered with FDA, Quantum Leap Healthcare, and the UCSF-Stanford Center of Excellence in Regulatory Science and Innovation to launch OpenClinica Unite for EHR to EDC integration, and OpenClinica Share for patient-directed health record sharing. With over 10,000 studies and counting, we have supported clinical trials on six of the seven continents spanning Phase I-Phase IV research as well as academic studies.

www.openclinica.com

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Clinical Trial Data Capture is slow and costly

The capture and management of clinical trial data is notoriously time-consuming and expensive, largely a result of the need for manual abstraction of data from electronic health records (EHR).[1–3] A large portion of data stored in EHRs is in the form of clinical narratives rather than discrete information fields. Completion of a study's electronic Case Report Forms by abstraction introduces serious quality issues, as it is highly susceptible to transcription error, resulting in median error rates that are an order of magnitude higher than other data processing methods.[4,5] These high error rates necessitates additional resource expenditures for source data verification (SDV), in which individual data fields in the transcribed trial records are compared against the original EHR source data. This results not only in significant costs, but also impedes timely availability of patient-level data that may be critical during times of public health emergencies.

Harmonizing Clinical & Research Data Management is a Priority

In 2013, the Food and Drug Administration (FDA) published the 'Electronic Source Data in Clinical Investigations (eSource)' guidance.[6] This guidance was intended to promote the capture of source data in electronic form to improve the reliability, quality, integrity, and traceability of data from electronic source to electronic regulatory submission. With the increased adoption of health IT systems and interest in using Electronic Health Records (EHR) as a source of Real-World Data (RWD) in clinical investigations, the FDA published guidance on the 'Use of Electronic Health Record Data in Clinical Investigations' in 2018.[7] The goal of this guidance is to facilitate the use of EHR data in clinical investigations and promote the interoperability of EHR and Electronic Data Capture (EDC) systems.

Following the release of FDA guidances, investigators at the University of California San Francisco (UCSF)-Stanford University Center of Excellence in Regulatory Science and Innovation (CERSI), in collaboration with the FDA, initiated a project to investigate solutions to one of the 2018 guidance's key goals - establishing a framework for interoperability and reliable, secure transfer of data between EHR and EDC systems.

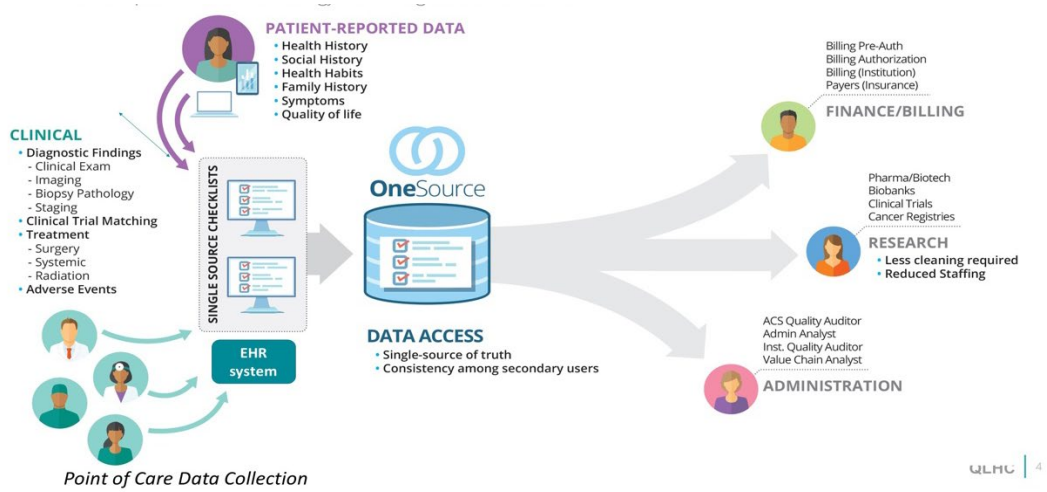

Figure 1: OneSource vision of structured data collection at the point-of-care, creating a single source of truth that permits easy, rapid re-use of data for multiple purposes.

OneSource Features

OneSource automates the flow of structured EHR data into data systems supporting clinical trials (although other secondary uses of these data are also possible). Reducing and/or eliminating manual processes minimizes the need for data adjudication between sites and sponsors, improves data completion rates and thereby reduces costs and burden for health care providers, and research staff, improves data quality and clinical care.

OneSource is designed to be deployable across heterogeneous sites and trials. It supports integration with Epic and Cerner EHR systems, using a recognized security model, requires no software installs, and implements a user-driven and audited model for data transfers - SMART (Substitutable Medical Applications and Reusable Technologies) on FHIR (Fast Healthcare Interoperability Resource). This reduces burden and risk on hospital IT and security staff, currently a major barrier to eSource. The EDC's study design tools allows data mapping updates with audited publishing and change control - ensuring data integrity without involving site research or IT staff.

EHR integration provides research site personnel with user-centric EHR-integrated workflows and automated data acquisition (Figure 2), minimizing many of the inefficiencies and quality risks of today's 'swivel chair interoperability' practices. The eCRF can be launched from the patient chart with a single click. Structured data from the EHR populates the eCRF, with workflows for user review/validation. eCRFs that cannot be directly populated are accessible for manual entry. Mobile support enables direct data capture at the point of care. The EDC's proven 21 CFR part 11 compliant features support regulatory-grade evidence of data integrity.

Table 1: Software components leveraged as part of OneSource V2.

Component	Function
Electronic Data Capture (EDC)	Clinical research data entry system
Randomization Engine	Randomizes patients to study arm
ePRO	Patient facing survey platform
EDC reporting system	Reporting and dashboard system
Biospecimen Laboratory Information Management (LIMS)	Capture of specimen information and management of samples
Safety System	Adverse event safety database system
Milestone payment system	Automated site payment processing
Electronic Health Record (EHR to EDC) integration for Epic, Cerner and patient mediated access	Capture discrete data automatically into EHR

For a technical description of OneSource, eSource and solutions/barriers to EHR-EDC integration, see the OpenClinica/Quantum Leap submission to "Request for Information on Data Collection for Emergency Clinical Trials and Interoperability Pilot," FR Doc. 2022–23489.

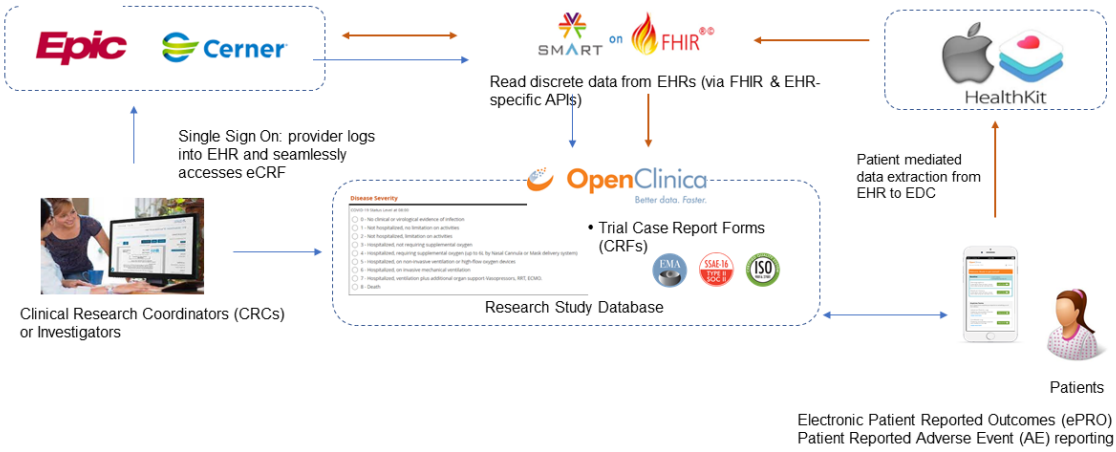

Figure 2: Framework for Investigators and Clinical Research Coordinators (CRC) accessing both clinical care and research systems seamlessly within one interface at the point of care. Patient Electronic Reported Outcomes (ePRO) support remote patient quality of life and patient reported adverse events using standardized survey instruments.

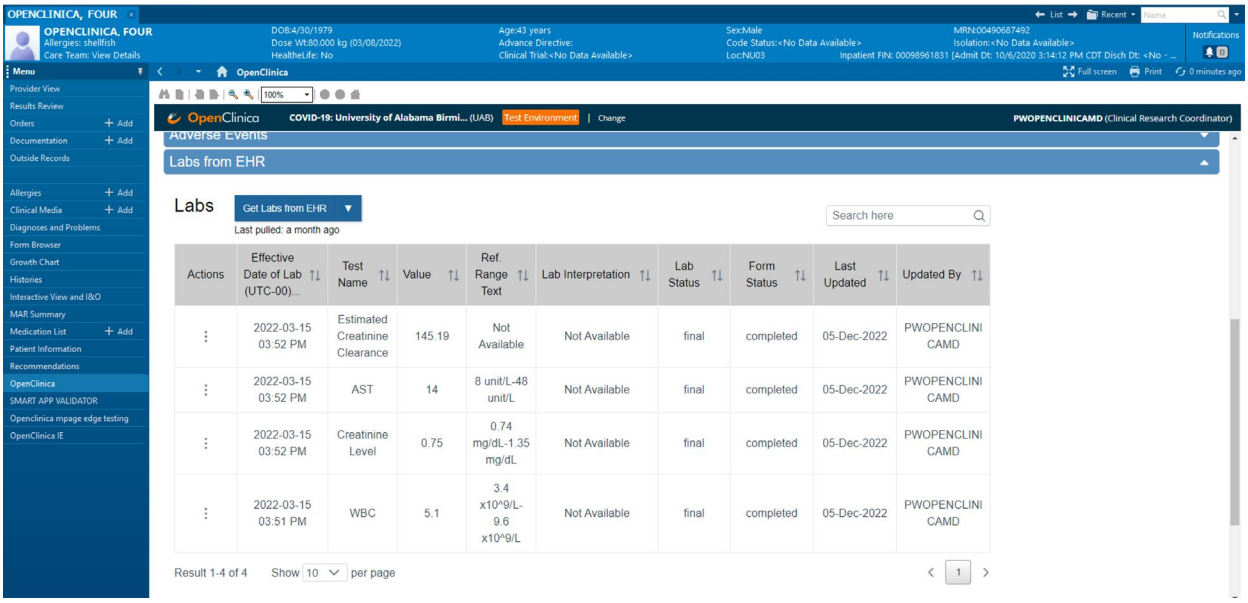

Figure 3: OneSource is embedded within the EHR system allows end-users to seamlessly auto-capture laboratory data within a patient record by clicking the "Get Labs from EHR" button. Laboratory data from the EHR are displayed.

OneSource Benefits Demonstrated in the I-SPY COVID Trial

The initial production instance of OneSource was deployed at 8 of 30 clinical sites in the I-SPY COVID trial, a platform trial evaluating repurposed therapeutics for severe acute respiratory distress syndrome (ARDS) caused by COVID-19 (as of December 2022, OneSource was in active use at 15 clinical sites in the ongoing trial).

Prior to deployment, study investigators established a consensus ‘checklist’ of critical clinical data elements required for study purposes. Approximately 30% of required data elements were already captured within the EHR as structured data and were configured to permit automated capture from the EHR to EDC through OneSource; these included patient demographics, laboratory data and concomitant medications. Deployment and configuration of OneSource at individual I-SPY COVID sites required an average of 15-20 hours of site personnel time, with similar requirements in informatics in environments utilizing Epic or Cerner EHRs, either cloud-based or locally hosted.

In the standard workflow for automated data capture from the EHR, clinical research coordinators (CRC) launch OneSource through a tab in a patient’s EHR chart (linked via FHIR ID). Once in the app, research/eCRF data & EHR records may be viewed side by side, users can perform manual eCRFs data entry where needed, and automatically populate configured eCRFs using data automatically pulled from the EHR with a single click, including patient demographic, lab, and medication data. OneSource is fully auditable, maintaining detailed transaction logs and the EDC’s proven 21 CFR part 11 compliant features support regulatory-grade evidence of data integrity.

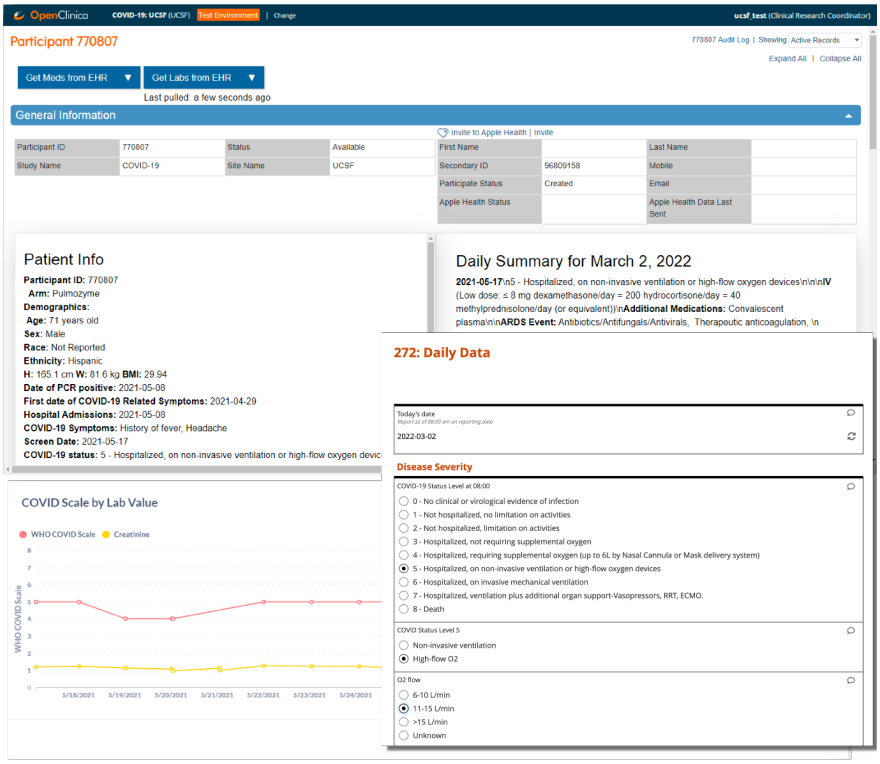

Figure 4: OneSource user interface launched directly from the EHR using the “OneSource” tab. Buttons on top automate extraction of laboratory results and concomitant medications by CRCs. Investigators have additional decision support displays that summarize the patient summary and the daily summary for the patient that can be rapidly tabbed across days to review progression. Additional graphical displays can be configured to show lab results, Adverse Events, and other research or clinical variables over time. For data entry, the daily data intake launches for data entry for the WHO clinical progression scale.

For OneSource sites with data entry metrics pre and post implementation, we discovered close to a

50% decrease in data entry times for case report forms associated with the primary end point. Transcription errors in these data elements were eliminated after implementation the use of OneSource, which resulted in additional downstream time/effort savings by eliminating the need for source data verification and improving the timeliness of data availability.

OneSource has also enabled the I-SPY COVID trial to establish an observational arm that collects registry information for an observational arm for patients who do not consent to participation in the randomized trial (under a IRB-issued waiver of consent) that currently has over 2000 patients.

Current Development Priorities

The UCSF Breast Care Center has established its own in-house structured data specifications for breast health, and currently uses OneSource for the routine collection of structured data as part of routine clinical care and associated research. Data collected form the platform is used for a number of interventional studies and registries including: Phase 1b, I-SPY 2.2, DCIS and others.

As part of this effort, OneSource is being configured for the automated capture of adverse event reports in the breast care center, using the National Cancer Institute's Common Terminology Criteria for Adverse Events[8] (CTCAE) along with the associated Patient Reported Outcomes version of CTCAE (PRO-CTCAE).[9] Additional development priorities include enabling automated EHR-EDC transfer of structured pathology data, using the College of American Pathologists' electronic Cancer Checklists which are now used by 35-40% of pathologists in North America and whose data is widely accepted by cancer registries.[10–12]

How OneSource Supports Warm Base Research & Emergency Trials

OneSource is envisioned to work in tandem with US Core Data Interoperability (USCDI) efforts to establish interoperability standards and implementation specifications for clinical, public health, and research purposes. QLHC in partnership with UCSF submitted proposals in September 2022 to the United States Core Data for Interoperability (USCDI) V4 data elements.

Table 2 (next page) summarizes a possible use case and associated benefits of OneSource in the pre- and post-emergency periods.

Implementing OneSource structured data capture at the point-of-care during the pre-emergency period will establish the necessary infrastructure, resources, and trained personnel to enable rapid deployment of clinical trial data systems when a public health emergency warrants. Pre-emergency use of OneSource would also provide the infrastructure to establish 'peace time' registries that could provide baseline data that could inform the early response to the emergency. Furthermore, the registry would provide critical data in the early period of the emergency, prior to clinical trial initiation, that would provide insight into the efficacy of on/off-label treatments.

Table 2: High level overview of possible OneSource use case for rapid trial deployment in response to public health emergency

Pre-implementation (pre-emergency)
OneSource platform already established at 20+ sites nation wide
Leverage current USCDI standard data elements used as part of FHIR data resources. If new elements required, propose as required for broader meta data
Design Library of EHR/OneSource electronic data capture forms using standard SMART on FHIR to CDISC standards mappings
Reconcile data standards
Develop standardized biospecimen infrastructure with integrations (OpenSpecimen) to OneSource platform for preparation, handling and shipping requirements
Reconcile data standards overlap, redundancy, collisions (LOINC codes for labs), FHIR resources using ICD10 vs SNOMED, etc.
Safety platform (Oracle Argus) integrated with OneSource
Implementation (pre-emergency)
Conduct Health Informatics Environment Assessment at each site
EHR integration and structured capture setup for new sites
EHR/EDC Interoperability Training
Biospecimen sample collection training
Inter-emergency period (pre-emergency)
Consensus and curation of EHR/OneSource electronic data capture forms using standard SMART on FHIR to CDISC standards mappings
Sites capture structured USCDI data as part of regular clinical care
Registry data pulled from EHR at regular (weekly) intervals & uploaded to central repository
Governance/Oversight body runs regular monitoring reports, conducts registry studies as needed
Collect coded biospecimens for registry/repository with consent
Early Emergency
USCDI data elements collected through registry provide immediate access to data/outcomes of all treatment courses and on/off-label therapeutics used
Registry provides baseline data for related conditions/complications
Trial Implementation
Seamless, overnight implementation of trial eCRFs - based on USCDI + additional elements as required; minimal change in clinical data workflows required (single click data transfer from EHR, just as with registry)
Consent, randomization, biospecimen and repository implementation at each site; requires minimal additional training as procedures remain consistent with pre-emergency clinical data/specimen workflows (only randomization, updated consent)
Trial Operation
Physicians/clinical support staff continue to collect data as per pre-emergency clinical data workflows
eCRF completion via single click (can you do bulk transfers based on enrollment in trial?)
Daily upload of de-identified data to central repository

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1. Rossetti SC, Rosenbloom ST. Report from the 25 by 5: Symposium series to reduce documentation burden on US Clinicians by 75% by 2025. Published online August 6, 2021. Accessed January 23, 2023. https://www.dbmi.columbia.edu/wp-content/uploads/2021/12/25x5_Executive_Summary.pdf

2. Siegler EL, Adelman R. Copy and Paste: A Remediable Hazard of Electronic Health Records. *The American Journal of Medicine*. 2009;122(6):495-496. doi:10.1016/j.amjmed.2009.02.010

3. Kalra D, Schmidt A, Potts H, Dupont D, Sundgren M, Moor GD. Case Report from the EHR4CR Project—A European Survey on Electronic Health Records Systems for Clinical Research. *Health Connections*. 2011;1(2):108–113. https://www.researchgate.net/publication/261286987_Case_Report_from_the_EHR4CR_Project-A_European_Survey_on_Electronic_Health_Records_Systems_for_Clinical_Research

4. Zozus MN, Pieper C, Johnson CM, et al. Factors Affecting Accuracy of Data Abstracted from Medical Records. *Plos One*. 2015;10(10):e0138649. doi:10.1371/journal.pone.0138649

5. Feng JE, Anoushiravani AA, Tesoriero PJ, et al. Transcription Error Rates in Retrospective Chart Reviews. *Orthopedics*. 2020;43(5):e404-e408. doi:10.3928/01477447-20200619-10

6. Food and Drug Administration. Electronic Source Data in Clinical Investigations. Published September 2013. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/electronic-source-data-clinical-investigations

7. Administration F and D. Use of Electronic Health Record Data in Clinical Investigations. Published July 2018. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/use-electronic-health-record-data-clinical-investigations-guidance-industry

8. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) | Protocol Development | CTEP. Published April 19, 2021. Accessed January 27, 2023. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

9. Basch E, Reeve BB, Mitchell SA, et al. Development of the National Cancer Institute's patient-reported outcomes version of the common terminology criteria for adverse events (PRO-CTCAE). *Journal of the National Cancer Institute*. 2014;106(9):dju244-dju244. doi:10.1093/jnci/dju244

10. Torous VF, Simpson RW, Balani JP, et al. College of American Pathologists Cancer Protocols: From Optimizing Cancer Patient Care to Facilitating Interoperable Reporting and Downstream Data Use. *Jco Clin Cancer Informatics*. 2021;5(5):CCI.20.00104. doi:10.1200/cci.20.00104

11. Simpson RW, Berman MA, Foulis PR, et al. Cancer Biomarkers: The Role of Structured Data Reporting. *Archives Pathology Amp Laboratory Medicine*. 2014;139(5):587-593. doi:10.5858/arpa.2014-0082-ra

12. North American Association of Central Cancer Registries. Standards for Cancer Registries Volume V: Laboratory Electronic Reporting for Pathology ver 5.0. Jones S, Mazuryk J, Havener LA, eds. Published online May 2020. Accessed January 25, 2023. https://www.naaccr.org/wp-content/uploads/2020/07/NAACCR-Vol-V_Revised_20200720.pdf

RFI Response: Clinical Research Infrastructure and Emergency Clinical Trials

Organization filing this comment: Duke University
Point of contact: Susanna Naggie, MD, MHS, Professor of Medicine, Vice Dean for Clinical Research, Duke University School of Medicine (susanna.naggie@duke.edu)

OSTP Request for Information: Clinical Research Infrastructure and Emergency Clinical Trials

Reference: Federal Register Notice: Document Citation: 87 FR 64821 // Page: 64821 – 64824 (4 pages) // Document Number: 2022-23110

Submitted Electronically on January 27, 2023: To emergencyclinicaltrials@ostp.eop.gov (Grail Sipes, OSTP)

Duke University is a major research university, and the Duke School of Medicine (SOM) is ranked number six for research among medical schools in the 2022 annual US News & World Report ranking. Duke is placed third nationally among academic medical centers in federal funding from the National Institutes of Health (NIH). Duke is home to the Duke Clinical Research Institute (DCRI), the world's largest academic clinical research organization. Duke University Health System (DUHS) is comprised of three hospitals and has an extensive, geographically dispersed network of outpatient facilities that include primary care offices, urgent care centers, multi-specialty clinics and outpatient surgery centers. Duke SOM had $860M in sponsored research expenditures in fiscal year (FY) 2021, and 24,700 patients participated in more than 2,280 active studies in FY2022. As an institution, we have extensive experience in leading research networks, acting as a coordinating center, and enrolling participants in site-based research. We are pleased to offer these comments in support of the OSTP effort to ensure that coordinated and large-scale clinical trials can be efficiently carried out across a range of institutions and sites to address outbreaks of disease and other emergencies.

1. Governance for emergency clinical trials response.

b. Criteria that should be applied in determining when coordinated and potentially large-scale clinical research is needed.

Ideally, a global surveillance system would identify potential threats and in response coordination would begin before the World Health Organization (WHO) declares a global emergency. We must be prepared to act rapidly when there is a novel and/or high threat pathogen that is easily transmissible. Respiratory viruses are the most obvious, including new flu strains, which continues to be the most likely etiology of the next pandemic. We need a structure consisting of acknowledged experts charged with addressing potential threats. The experts would verify if it is a real threat, if it is likely to escape, and whether we can implement research within weeks. "A Global Early Warning System for Pandemics: A Blueprint for Coordination" published by the Milken Institute thoughtfully outlines criteria to consider[1].

It is also critical to consider and support/maintain the various types of studies that have been critical in informing the COVID-19 response. During the COVID-19 pandemic, much of the data on vaccine effectiveness, persistence of immunity, and viral variants has been captured through established national health system databases (e.g. U.K., Israel, and Qatar). A national trials network in the U.S. which aggregates electronic health record (EHR) data would facilitate reporting of real-word evidence for

emerging pathogens and variants. This resource would provide timely evidence to support the value of interventions, specifically among the diverse U.S. population, to drive policy efforts and public health guidelines. While there is also a large role for prospective clinical trials, due to the nature of large trials, the ability to respond in real time to a rapidly changing pandemic has proven to be difficult. Thus, ensuring a combination of research study design, including prospective cohort development through existing and extensive data resources, will be critical.

f. Procedures whereby the U.S. Government, together with external stakeholders, could oversee the development of clinical trial protocols and, where appropriate, the selection of investigational agents.

We recommend centralized top-down coordination with clear prioritization from the NIH for future threats. Due to the need to be able to respond rapidly, it is critical to have a structure consisting of acknowledged experts that would evolve over time.

- Alignment across all institutes and branches of the NIH will be critical for the most efficient protocol development and operationalization
- Due to the need to move quickly and address the most critical questions to improve the health of the public and prevent significant morbidity and mortality, the protocols should focus on key clinically relevant objectives. While it is of great interest to design studies that gain insight into epidemiology and pathogenesis, a primary focus, particularly of the first clinical trials, should focus on objectives that are the most clinically relevant to immediately improve the clinical outcomes of the novel disease and that are the most immediately translated into clinical care. This is not intended to under estimate the importance of epidemiology and pathogenesis studies; however, the timeline for achieving the primary clinical outcomes should not be impacted by these additional objectives.
- Although the COVID-19 response focused on leveraging existing networks with the expectation that this would accelerate timelines for start-up and study accrual, this was not necessarily the reality for all studies. It is critical that the reasons for these delays be identified and addressed, or that rapid accelerator networks be developed that will not have the same pitfalls and challenges.

Public-private partnerships were critical to getting COVID-19 vaccines and therapeutics into trials and authorized quickly. Collaborations such as the Adaptive COVID-19 Treatment Trials (ACTT), and the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) were very successful. For example, Gilead's willingness to partner was critical to rapidly starting the initial trials with remdesivir for COVID-19. Public-private partnerships are needed with a master registry protocol "at the ready" that can be immediately deployed to start collecting data to inform natural history, transmission patterns, the characteristics of the population at the greatest risk. We suggest similar approaches should occur with diagnostics.

We recommend centralized, pre-positioned funding be immediately available or pilot or seed funding that can go to industry and academic partners to begin early trials or develop new diagnostic tests. This commitment would come with the acknowledgement that funding may be "lost" if the threat fades away, which is an acceptable cost of being ahead of the response. The benefit of such funding was clear for COVID-19 which allowed for rapid startup of the remdesivir trials. In contrast, the lack of such funding for monkeypox delayed trial start-up.

g. Best practices, including "quality by design" principles, for designing trials so that they capture the data needed without unnecessary complexity that can complicate execution.

"Quality by design" principles outlined in advance would be a good start. These principles would include minimizing inclusion/exclusion criteria; allowing for flexibility in visit location (research site, remote, home, mobile); allow e-consent; have platform protocols '"at the ready"; have registries infrastructure ready for detailed pre-screening prior to enrollment; draw data from EHRs whenever possible; assemble a list of devices/procedures that can be done at home and are allowable/authorized per FDA; partner with FDA in advance to clarify where there is flexibility in assessments and tele-research laws.

h. Best practices for designing trials that can enroll vulnerable populations, such as the pediatric population, as needed in particular circumstances.

Best practices to consider include partnerships with community-based organizations to access vulnerable populations; ensure experts are consulted when designing trials in vulnerable populations; engaging the FDA early when thinking of vulnerable populations; and limiting assessments and procedures to ensure vulnerable populations can be enrolled. There were considerable resources devoted for many large-scale COVID-19 vaccine trials for adults. Unfortunately, trials for children were not prioritized and studies in pregnant women were few. There should be networks of research sites able to do studies in children, pregnant women and other populations, poised to start trials earlier in the process.

k. Appropriate ways to structure a data repository and a biorepository for emergency clinical trial data and specimens. As noted above, one potential model would be to collect data and biospecimens in centralized repositories. We would also appreciate input on whether existing entities could be engaged or adapted to handle these repository functions.

Knowledgeable, trained research staff are needed to collect specimens in different environments, such as inpatient, outpatient, or in homes in the face of a larger pandemic threat. Specimen processing should be limited to centralized processing cores that have appropriate safety protocols, trained laboratory staff, and use validated, standardized methodology and protocols that reduce non-relevant variability in results. Specimen data should be managed in a centralized Laboratory Information Management System (LIMS). A centralized LIMS ensures consistent data terminology and variables are utilized, and provides higher feasibility for combining the specimen data with EHR data. Maintaining sites with this expertise across the country and/or globe would allow for the rapid collection of biospecimens with collection of associated high quality clinical data. In this setting there would also be a need for master service agreements across the network to ensure ease of sharing specimens and data to accelerate the discovery.

Ideally these sites would have existing general infection protocols that would allow for the rapid and real time procurement and collection of biospecimens for the novel infection and only the need for protocol modifications to add clarifications as needed for the novel disease/organism.

Centralized funding for institutional biorepositories should be considered. Most institutions that develop COVID-19 biobanks, did so on institutional funds which resulted in many cases in limited resources to complete the more comprehensive collection that would have been desirable. This more ad hoc and local development likely results in resources spent for suboptimal end product. Planning now for a biobanking network would likely improve financial and operational efficiency.

2. Identifying and Incentivizing Research Institutions and Networks; Building Diversity and Equity.

a. Methods for identifying institutions and sites that may have an existing interest in or familiarity with emergency clinical trial research. This might include those that currently receive government funding, those with a focus on infectious disease research, and/or those that have worked with CROs.

The current pandemic response has provided insight into the successes and challenges of standing up clinical research infrastructure in the setting of a national emergency. The approach of leveraging existing networks in concept made sense although at this time it is unclear if this was the most efficient approach and there is concern that it was not an effective approach to ensuring diverse representation and access to clinical trials.

For future responsiveness, a ready infrastructure needs to be in place at institutions and health systems across the country in order to respond to emergency clinical trials. The network of networks approach has limitations due to the large concentration of existing federally funded networks at major research institutions that may not reside in rural and underserved/marginalized communities. An approach to assess interest in research should be driven by a goal of achieving diversity in enrollment. Identifying the communities and populations that are critical for representation in clinical trials and should be a primary method of identifying sites for inclusion in a warm network of clinical trials.

b. Effective ways to increase diversity among study participants and investigators, and to expand clinical research sites into underserved areas.

Engaging sites beyond academia is important to reach underserved and rural communities. Community-based trials initiatives such as Rapid Acceleration of Diagnostics – Underserved Populations (RADx-UP) have demonstrated that the presence of local trusted voices was critical to encouraging COVID-19 testing and vaccination and will need to be a key element of engagement for future trials and pandemic response. Creating community trials networks that include non-academic and safety-net hospitals, pharmacies, and public health departments are key to diversification, and should be supported and sustained during inter-pandemic times as an essential component of the "warm" trials' infrastructure. Community-based clinicians and Federally Qualified Health Centers often have established and trusted relationships with communities, increasing the likelihood of trial participation among underserved populations and improving equity in access to trials[2]. Forming trusted relationships with communities is key and hence engagement with community leaders is critical and necessary to ensure there are trusted voices in dissemination of information, particularly early in pandemic response when there is rapid evolution of knowledge and discovery.

Decentralized trials/hybrid trials or "direct-to-participant" trials are also critical to expanding trial access and diversification[3]. The ACTIV-6 (COVID-19 Study of Repurposed Medications) platform trial leveraged telemedicine, direct-to-participant delivery of study drugs and materials to patients' homes, and remote collection of participant-reported outcomes, limiting the need for in-person contact between the study team and the participant. These methods center the participant in clinical trial design and reduce patient participation burden while allowing for the attainment of robust outcomes.

e. The best ways to provide training in clinical trial practice (including regulatory requirements such as Good Clinical Practice (GCP)) where needed, targeted as appropriate to staffs' roles, including staff at sites that may not have participated in clinical trials previously.

Easy, fit-for-purpose training that is tailored depending on the experience of the site is needed. Some sites will need more extensive training, and other sites will need less. In order to achieve the goals of rapid start-up and diversity in sites and in the populations recruited, the barriers for sites will need to be lowered. Trials like ACTIV-6 and pragmatic trials, which are more closely aligned with clinical best practices, should be models for finding the balance between compliance and safety and inclusion.

One priority that is critical for training research staff is need training on equity, diversity, and inclusion; unconscious bias. Just ASK™ is a training which provides a health equity framing and lens that can be completed independently in about 60-90 minutes, and focuses on the broader context of structural and systemic racism. This training has been adopted by national associations and is likely to become a best practice for research training.

3. "Warm Base" Research.

a. Disease areas that should be targeted in protocols for "warm base" clinical research.

Ideally targeted disease areas for warm based clinical trials will be community driven. Developing methods by which communities can surface the research questions most critical for their health would result in a win-win. For example, NIH is starting the Community Partnerships to Advance Science for Society (ComPASS) in 2023. The goals of ComPASS are to "1) develop, share, and evaluate community-led health equity structural interventions that leverage partnerships across multiple sectors to reduce health disparities and 2) develop a new health equity research model for community-led, multisectoral structural intervention research across NIH and other federal agencies"[4]. These types of efforts should be expanded.

The RFI did not mention addressing the systemic sectors that drive health, such as access to healthcare, employment, urban development, economics, etc. These are areas that we also need to consider, not just disease-specific needs.

b. How "warm base" research could best be implemented to provide training to sites that are inexperienced with clinical trial research, and to create a basic level of surge capacity at the staff level for emergency clinical trial research. We would appreciate input on other training mechanisms that could be used as well.

c. Whether "warm base" research could be appropriately supported as

i. A demonstration project with commercial partnership.
ii. A public-private partnership.
iii. An agency-funded program.

Investing in and maintaining operational "warm base" clinical trials infrastructure, diagnostic capabilities, manufacturing capacity, and supply chains maximizes the readiness to enroll participants in clinical trials and allows agile trial networks to respond quickly to changing incidence. Public-private partnerships are important here, as there are many companies working on addressing site preparedness/capacity that can be leveraged. In addition, direct-to-participant approaches could be included here (Topography, Sitebridge, Science 37, Hawthorne Effect, Lightship, Recognition Health, etc.).

"Warm base" research capacity should leverage point-of-care approaches. Such approaches have the potential to increase the ability for an emergency clinical trial network to capture the data needed without unnecessary complexity that can complicate execution due to its simplified protocols.

Open, approved protocols that allow one to "fill in the bug and the drug" are needed. For example, the Strategies & Treatments for Respiratory Infections & Viral Emergencies (STRIVE) is a new clinical trials platform funded by the NIH and is intended to be for new viral pandemics that involve pulmonary critical care components.

4. Emergency Master Agreement.

c. The best ways to get the input of research institutions, clinical researchers, community groups, and other key stakeholders on the content of Emergency Master Agreement terms.

The NIH ComPASS and Community Engagement Alliance (CEAL) programs already exist to engage communities in research. These groups should be engaged in discussions on how to leverage existing and future infrastructure.

d. Approaches to facilitating stakeholders' understanding and adoption of the Emergency Master Agreement framework.

i. Any models for such adoption in related areas, such as the NCATS SMART IRB Platform.

We need established sites with template agreements. The National Center for Advancing Translational Sciences (NCATS) Streamlined, Multisite, Accelerated Resources for Trials (SMART) IRB platform is steamlining the IRB review process. We would benefit from a similar approach for master agreement terms.

6. International coordination and capacity.

International preparation requires identifying trusted and resourced centers. Pre-existing relationships can be leveraged for early responses to emerging public health threats, such as timely sharing of global clinical samples for rapid development of diagnostics, therapeutics, and vaccine development. Global clinical research organizations (CRO) generally have these existing relationships, and that relationship is important for contracting and regulatory needs. Creating these contracts and agreements now and formalizing diverse networks from the partnerships that have developed over the past two years, is key to accelerating the rapid scale-up of discovery needed to respond early and swiftly to the next pandemic.

Broad geographical distribution makes sense and provides flexibility as global diseases may bounce between countries. In mid-2020, the COVID-19 cases dropped in the US, and it gave some of the networks time to get formed and enroll in large numbers during the delta and omicron waves.

International trials that include countries with a single payer system, such as the United Kingdom, were able to rapidly enroll and share data. The U.S. should develop a single national system of trial participants, drawing from linked electronic health records (EHRs), to allow rapid randomization of large numbers of participants into definitive clinical trials. The National COVID Cohort Collaborative (N3C), an open science community that aims to aggregate and harmonize EHR data across clinical organizations in the U.S., is an example of a novel partnership for collaborative data sharing that could

be used to address key clinical questions in future health emergencies. A unified clinical trials network would also incentivize companies with candidate drugs and biologics to participate, through the ease of centralized laboratories, data and safety monitoring boards, and access to large participant numbers and increasing statistical power for definitive endpoints.

References:

1. Krofah E, Choe SH, Sud A, et al. A global early warning system for pandemics: A blueprint for coordination. The Milken Institute; 2022. Accessed at https://milkeninstitute.org/sites/default/files/2022-03/Global%20Early%20Warning%20for%20Surveillance_FINAL.pdf on 23 December 2022.
2. Woodcock J, Araojo R, Thompson T, et al. Integrating research into community practice - toward increased diversity in clinical trials. N Engl J Med. 2021;385(15):1351-1353.
3. Van Norman GA. Decentralized clinical trials: The future of medical product development? *. JACC Basic Transl Sci. 2021;6(4):384-387.
4. Community Partnerships to Advance Science for Society (ComPASS). Accessed at https://commonfund.nih.gov/compass on 23 December 2022.

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January 27, 2023

The White House
Office of Science and
Technology Policy

Re: Request for Information (RFI) on Clinical Research Infrastructure and Emergency Clinical Trials

Dear Recipient:

The Biotechnology Innovation Organization (BIO) thanks The White House OSTP and National Security Council for the opportunity to submit comments regarding the Request for Information (RFI) on Clinical Research Infrastructure and Emergency Clinical Trials.

BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO's members develop medical products and technologies to treat patients afflicted with serious diseases, to delay the onset of these diseases, or to prevent them in the first place.

BIO greatly appreciates the opportunity to share industry's expectations regarding clinical trials with decentralized approaches in the following four subsections.

I. State Licensure Barriers to Optimal Decentralized Clinical Trials

Clinical trials with decentralized features have the potential to improve clinical trial access by engaging more people in research, increasing trial opportunities for under-represented populations, and enhancing flexibility for participating in a trial for geographically remote participants and investigators, or participants who face difficulties traveling to clinical trial sites. Additionally, clinical trials with decentralized features also improves patient retention and adherence to study procedures. Decentralized features could include recruitment through a digital campaign, trial participants using a digital health technology to remotely collect data, telehealth visits, home nursing, leveraging local clinical sites for certain in-person clinical assessments and/or procedures – physical exams, specimen collection (and occasionally analysis), diagnostic and prognostic procedures (such as imaging, scans) and direct-to-patient shipment of the investigational product.

In the United States, state medical licensure disparities are limiting the ability to recruit patients from various states. In a full expression of a DCT approach sponsors of clinical trials would be able to reach a potential patient anywhere in the U.S. and enroll them into a virtual trial. However, there could be a case where a patient resides in a different state from where the clinical investigator holds their medical license, there-by posing a challenge to a full expression of a DCT approach.

Medical licensure is regulated at the state level, but investigational clinical trials and their conduct are regulated at the federal level. State licensure requirements can place a barrier on decentralized clinical trials, as a virtual site (a.k.a. *meta site*) would need to have investigators on staff that are licensed in all 50 states. In response to the Covid crisis many states modified licensure requirements for health care providers, including out-of-state requirements for telehealth. Although these measures were welcomed by industry, physicians, and patients, they were temporary in nature and many states are now pulling back and starting to revoke them. To strengthen U.S. capacity for conducting clinical trials, we need to revisit state medical licensure processes currently in place and develop more permanent solutions.

BIO offers the following possible approaches to addressing these licensure barriers:

- Flexible reciprocity schemes, such as the Interstate Medical Licensure Compact[i], can facilitate the running of trials across multiple states. The Compact is an agreement among states who want to significantly streamline the licensing process for physicians who want to practice in multiple states. The mission of the Compact is to increase access to health care, particularity in underserved and rural areas. To drive participation in such schemes, the federal government might consider incentives for states who opt-in to such programs like specially allocated funds which support the further adoption of telemedicine and associated capabilities (e.g., broadband/IT infrastructure).

- Another approach that could have a positive impact includes federal and state legislation that would differentiate the practice of medicine and clinical trials. For example, limited waivers could be created for clinical trials.

- Additionally, in an emergency clinical trial setting, it may be likely that sponsors leverage direct-to-patient shipment of the investigational medical product (IMP) to alleviate risks of in-person consultations and assist patients who have limited transportation or mobility issues. Several sponsors employed such tactics during Covid-19 to mitigate risk of exposure to the virus. Ensuring that state pharmacy boards do not place an undue burden for vendors seeking licensure in states to ship IMP would be another consideration for ensuring a robust infrastructure for the conduct of emergency clinical trials.

- Finally, federal and state legislation that would ease or remove these licensure barriers could be another approach. Federal legislation, such as the Equal Access to Care Act[ii], introduced in response to the Covid crisis to provide for a broader application of telehealth visits, may be a viable model to build on that provides for telehealth across state lines.

II. Interagency Governance in Public Health Emergencies

Collectively, HHS and its sub-agencies are essential in spearheading the government's basic, clinical, epidemiological, behavioral, and translational research. Administration for Strategic Preparedness and Response (ASPR) and Biomedical Advanced Research and Development Authority (BARDA) also demonstrated their leadership in partnering with the private sector to conduct advanced research, expand manufacturing capacity and deploy resources in a time of crisis. However, determining which agency was accountable for specific activities and which group had available funding to pursue these efforts often led to delays and confusion during the COVID-19 Public Health Emergency (PHE). BIO is concerned that merely requiring consultation between agencies is insufficient to resolve these key challenges to proactively prepare for future pandemics. We therefore urge consideration on the following points:

1. The newly created White House Office of Pandemic Preparedness and Response Policy (as part of the end of year omnibus package (sec. 2104)) is responsible for the development and implementation of the national biodefense strategy - we believe the office should seek input from industry and other stakeholders on implementation of the plan.

2. There is also an opportunity for the newly created White House Office of Pandemic Preparedness and Response Policy to delineate accountabilities of each agency to avoid potentially redundant programs, efficiently allocate resources, and clarify decision making for partners and the public. Such delineations could be facilitated via the Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) to establish new accountability and decision-making authority to the Enterprise.

Throughout the COVID-19 PHE, BARDA has not only partnered to deploy and scale manufacturing capabilities but overseen complex advanced research projects to deliver next generation medical countermeasures (MCMs). To effectively manage the lifecycle of MCM discovery, development and sustainable procurement, BIO recommends that BARDA and programs like BioShield must be adequately resourced and delegated the necessary authority to enable the availability of MCMs in advance of when a public health threat emerges.

III. Clinical Trial Inclusivity and Impact on Underrepresented Populations

We appreciate OSTP's acknowledgement of the need to modernize clinical research as noted in the RFI section *Identifying and Incentivizing Research Institutions and Networks; Building Diversity and Equity*, and believe flexibilities and lessons learned through this pandemic provide a foundation on which to build. The use of digital technologies, including telehealth and remote monitoring devices, proved critical to the continued participation of patients in these trials, and allowed important research to continue.

Outside of the pandemic context, digital technologies and broader use of decentralized trial designs can also help address the historical underrepresentation of minority and other patient groups in clinical research. We support engaging with the FDA to encourage and increase use of such flexibilities during and beyond PHEs. We note that although the recently passed PDUFA VII and Omnibus contains provisions for FDA to issue guidances addressing some of these topics, there is value in engaging with the Agency on how these flexibilities can particularly be leveraged during a PHE.

IV. International Harmonization

BIO strongly supports harmonization of regulatory policy and action across reputable global health authorities - particularly with respect to manufacturing and inspections, as such coordination reduces conflicting or redundant work, resulting in less time and cost to bring treatments to patients. We encourage OSTP to work with FDA to explore expanded use of mutual recognition and mutual inspection reliance agreements, which currently are limited in scope. Additionally, we believe FDA should be encouraged and enabled to continue to play a leading role in the ICMRA Manufacturing Covid-19 lessons learned activities, to support future global responses and alignment.

BIO appreciates this opportunity to submit comments regarding the White House OSTP & NSC Request for Information (RFI) on Clinical Research Infrastructure and Emergency Clinical Trials. We would be pleased to provide further input as needed and we look forward to future opportunities to engage with the White House on this endeavor.

Sincerely,

Leslie Harden, Pharm.D.
Director, Science and Regulatory Affairs
Biotechnology Innovation Organization

[i] *The Interstate Medical Licensure Compact is an agreement among participating U.S. states to work together to significantly streamline the licensing process for physicians who want to practice in multiple states. It offers a voluntary, expedited pathway to licensure for physicians who qualify.*

[ii] Text - H.R.688 - 117th Congress (2021-2022): Equal Access to Care Act | Congress.gov | Library of Congress

COGR

An Association of Research Institutions

January 23, 2023

VIA EMAIL TO: emergencyclinicaltrials@ostp.eop.gov

RE: Response to Emergency Clinical Trials RFI

To Whom It May Concern:

The Council on Governmental Relations (COGR) is an association of over 200 public and private U.S. research universities and affiliated academic medical centers and research institutes. COGR concerns itself with the impact of federal regulations, policies, and practices on the performance of research conducted at its member institutions. One area of significant interest and expertise among COGR member institutions is the ethical conduct of clinical research involving human participants and the beneficial impact that findings from such research have on understanding and mitigating threats to public health. We write today to submit comments in response to the White House Office of Science and Technology Policy's issuance of the "Request for Information; Clinical Research Infrastructure and Emergency Clinical Trials" (87 F.R. 64821, Oct. 26, 2022), hereafter the "RFI."

The COVID-19 pandemic made clear the need for government agencies, research institutions, health care institutions, and pharmaceutical manufacturers to quickly launch clinical research during public health emergencies, as well as to broadly share and analyze the results of such research. COGR member institutions were on the front lines of many COVID-19 research efforts, and lessons learned from that experience can help inform preparations for future clinical research being conducted in similar emergency circumstances (hereafter "Emergency Clinical Research" or "ECR"). These lessons include the need to consider research from the patient/participant perspective, recognition of the fact that research can happen anywhere (patient home, community clinic, pharmacy), and that flexibility on the part of institutions and regulators is essential to ensuring that research can quickly "pivot" to address changing circumstances. COGR appreciates OSTP's issuance of the RFI to collect information for use in developing an Emergency Master Agreement framework to facilitate the conduct of Emergency Clinical Research, and we offer here responses regarding each of the broad topics set forth in the RFI.

1. ***Governance for emergency clinical trials response.***

As events during the COVID-19 pandemic illustrated, scientific progress toward understanding the virus and developing vaccines and treatments depended on the joint efforts of government, corporate, and non-profit entities. To address each of the items listed under this topic, COGR encourages OSTP to convene working groups that involve members from research funding agencies, clinical research regulatory agencies (e.g., Food and Drug Administration (FDA), Office for Human Research Protections (OHRP)), pharmaceutical companies, contract research organizations (CRO), research institutions, institutional review boards (IRBs), public health agencies, hospitals and other health care institutions (e.g., home health care organizations, pharmacies), and groups that represent the interests of clinical trial participants. In the heat of an emergency, research-intensive institutions may be more likely to take on research projects, but clinical entities may be so overwhelmed by the emergency that they are unable to engage in anything other than core clinical activities, and many also lack experience in conducting research and/or trained research personnel. Yet, emergency circumstances demand that clinical options be tested and deployed rapidly.

Accordingly, working groups should develop process maps that identify logistical and regulatory "choke points" and potential solutions that facilitate ECR across all types of institutions. Additionally, the groups should pinpoint factors that prevent sites and individuals from participating in clinical research, including financial and legal issues, such as subject injury costs or site liability/insurance issues. Non-traditional research sites that lack research-related compliance, risk management, and trial management infrastructure will be unable to address these issues amid a public health emergency, and, thus, to expand the site base, these items must be addressed before the next public health emergency. Analysis of these sticking points should identify existing regulatory flexibilities, as well as flexibilities that agencies can extend in emergency circumstances that can be leveraged to mitigate issues, and when such flexibilities are inadequate, regulatory changes should be considered.

2. ***Identifying and Incentivizing Research Institutions and Networks; Building Diversity and Equity, Subsections***

COGR supports OSTP's efforts to solicit recommendations on how to improve the diversity of both the sites that conduct ECR and the participants in that research, and we believe that certain existing projects and networks can be leveraged in this regard. For example, National Center for Advancing Translational Sciences (NCATS) supported Clinical Translational Science Awards (CTSA) program sites often have established relationships with the communities and patients that they serve. These relationships are particularly important in communities whose culture or history have engendered distrust of medical research. Research intensive institutions may be able to build on these relationships by facilitating the ability of other community health providers (e.g., community hospitals and clinics) to participate in ECR through a hub and spoke system, that

leverages the research institutions' expertise and infrastructure, while increasing outreach and broadening the participant base.

To promote these relationships, ECR participation roadblocks must be identified and eliminated, particularly for non-traditional research sites. For example, home health care agencies and pharmacies are often reluctant to participate in federally sponsored research activities if they must execute a Federalwide Assurance document or have staff undergo training in good clinical practices (GCP). Such requirements can limit participation in the best of circumstances, let alone in time critical research conducted during the height of a public health emergency, and their costs and benefits should be carefully considered in the ECR context, particularly when the activities being performed are substantially similar to clinical activities. We recommend that HHS work with OHRP to tailor the requirement for a Federalwide Assurance to the level of participation and engagement of community sites in emergency research.[1] Thought also should be given to whether additional flexibility is required regarding the application of the single IRB requirement in the context of ECR, where there may be tangible benefit to using local IRBs working directly in their communities.

In terms of incentives, we note that the RFI does not specifically discuss or seek information regarding funding needs. We respect this approach, as cost and budget considerations typically are handled on a project basis. However, COGR believes that it is critical for federal agencies to (a) identify areas in which the federal government can provide standing support that sites can tap to perform necessary functions in the ECR scenario; and (b) consider initiatives that will ensure the availability of appropriate clinical trial infrastructure in the event of a public health emergency. For example, the federal government's development, and on-going financial support, of a government maintained ECR data repository with associated electronic data collection tools would facilitate data collection and sharing, while eliminating a significant cost for sites and streamlining their trial budgeting. Government support for the development of technology for collecting data directly from electronic health records would also help build infrastructure that will facilitate participation by diverse sites in ECR.

3. ***"Warm Base" Research***

There are basic skills that cut across clinical research, no matter what type of disease/condition is being targeted: knowledge of applicable regulatory and GCP requirements; establishment of clinical investigations systems and processes; and data collection, analysis, and reporting. A warm base research approach must foster the development of these skills at potential ECR research sites and provide continuing support so that bases don't "cool." A program that utilizes the aforementioned "hub and spoke" approach could be developed to support experienced principal

[1] For additional discussion on the issue of "engagement" in research see COGR's July 8, 2022 letter to the Office of Human Research Protections (OHRP) and Secretary's Advisory Committee on Human Research Protections (SACHRP) in the record of the July 20-21, 2022 SACHRP meeting at https://www.regulations.gov/document/HHS-OASH-2022-0013-0016.

investigators and research coordinators at mature research sites in providing initial and continuing training to a core of research personnel at developing research sites to facilitate a state of readiness. Similarly, once an ECR protocol is initiated, seasoned investigators could be available for consultation with (or if the emergency is regional, perhaps deployment to) other research sites to assist with protocol-specific training and quickly bringing sites online.

A demonstration project would be an important first step in establishing a warm base research network, and perhaps leveraging existing networks such as the Community Oncology Research Program would provide an excellent avenue for such a project. COGR believes that agency funding of such a project is critical, but as it has done in the research security arena, OSTP should take the necessary steps to ensure that all involved federal agencies remain consistent in their award requirements. To do otherwise will undercut efforts to streamline ECR research and to promote diverse participation.

4. ***Emergency Master Agreement***

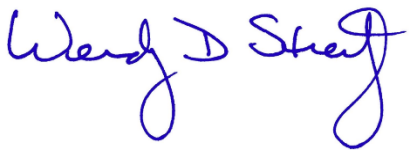
A user-friendly clinical trial master agreement that is acceptable to all research sponsors and sites without the need for multiple modifications has long been the "Holy Grail" of the clinical trial world. Fundamental differences in how public, private, for-profit, and non-profit entities can address complex issues such as data use, intellectual property rights, indemnification, and compensation for subject injury pose significant difficulties in the development of a one-size-fits-all contract. Nonetheless, certain groups have made great strides along these lines by developing contract templates that might be leveraged for use in ECR. For example, the FDP has developed a fixed rate clinical trial subaward template and associated guidance document with which many sites are familiar. In another effort, the Accelerated Research Agreements Initiative, organized working groups with representatives from research institutions and pharmaceutical companies and developed model clinical trial agreement forms including the Accelerated Confidential Disclosure Agreement, Accelerated Clinical Trial Agreement, and the CTSA Data Transfer & Use Agreement.

In developing a master agreement, consideration must also be given to the fact that non-U.S. institutions and companies may need to be involved for the ECR research to be fruitful. Global and political circumstances may make research institutions of all types reluctant to work with certain international partners, yet their information, data, and expertise may be essential to addressing the emergency. In such circumstances, OSTP and U.S. government agencies must be prepared to provide clear direction on any prohibited collaborations. Further, the development of mechanisms to foster rapid government-to-government communications regarding the emergency and ways to facilitate global ECR (e.g., international regulatory flexibilities) are essential.

Conclusion

COGR applauds OSTP's efforts to improve the nation's capacity to undertake ECR and to build on lessons learned from the COVID-19 pandemic. This will undoubtedly be difficult work, but COGR and its member institutions stand ready to assist in these efforts. We once again thank OSTP for this opportunity to provide our comments, and we hope that they will prove helpful. Should OSTP have any questions regarding this transmittal, please contact Kris West, COGR's Director for Research Compliance and Ethics at kwest@cogr.edu.

Sincerely,



Wendy D. Streitz
President

Federation of American Scientists

Strategies to Systematically Strengthen Clinical Trials Infrastructure

Thank you for the opportunity to provide information to the Office of Science and Technology Policy (OSTP) on key questions regarding state development of research infrastructure and processes for emergency clinical trials (ECTs). Overall success on this front requires success in a series of important stages: increasing federal capacity for collaboration within and across government; innovating to address technological limitations of existing infrastructure; improving participation through community-engaged research; issuing updated regulatory guidance for products developed through emergency trials; and investing in evidence synthesis, implementation, and communication. We refer to this as the I5 approach.

The Federation of American Scientists (FAS) is a catalytic, non-partisan, and 501(c)(3) non-profit organization committed to using science and technology to benefit humanity through policy agenda-setting and delivering on the promise of equitable and impactful policy. FAS believes that society benefits from a federal government that harnesses science, technology, and innovation to meet ambitious policy goals and deliver impact to the public. FAS brings together experts from science, engineering, political science, law, and policy in order to inform public policy. We hope to leverage our experience and networks of expertise to support the OSTP's efforts in this space.

Increasing Federal Capacity for Efficient Collaboration

This section will address questions relevant to building a centralized U.S.-level governance structure, focusing on designs that will be suitable for both pre-emergency coalition building and infrastructure development as well as emergency management (questions 1a, 1d, 1f).

The myriad extant partnerships across government agencies and external institutions provide a series of possible roadmaps for governance of an emergency clinical trials effort. The most common interagency efforts can broadly be structured as falling on a collaboration to coordination spectrum. Collaborative efforts—like the Interagency Council on Evaluation Policy—are those in which members participate in a given arrangement on relatively equal footing. Coordination efforts—perhaps the most significant example being the establishment of the Director of National Intelligence—are those in which one or two agencies or individuals are given authority and funding to shape and delegate cross-institution efforts. To build a governance structure that is positioned for success in both an emergency situation and public health "peacetime" requires components of each. Operation Warp Speed (OWS) offers valuable lessons for designing inter- and extra-agency partnerships that can meet both challenges.

OWS's efficiency and success during the early stages of the COVID-19 pandemic draws a direct parallel to the activities that would be required of a longer-standing emergency clinical trials structure during an acute emergency. OWS was established primarily as a joint partnership between the Department of Defense (DOD) and HHS, and leveraged several existing relevant

HHS offices and capabilities to provide guidance, data, and resources at various stages: the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), the National Institutes of Health (NIH), and the Biomedical Advanced Research and Development Authority (BARDA). This general structure ensured that OWS was a science-driven program backed by the organizational capacity and resources of the DOD. Further, it linked auxiliary offices to the effort without confounding the chain of command, securing buy-in from across the government.

OWS-like structures are maximally effective in situations where a pressing need and specific, time-bound goal can orient partner institutions towards a shared mission. Yet in order to address the many challenges that OSTP identified in this RFI, such a structure should be stood up well in advance of any emergency, and active programs of relationship formation, solutions R&D, community and research site engagement, regulatory innovation, and communication preparedness will need to be built. In "peacetime," with fewer external motivators, there is a risk of institutional ossification—such that member organizations may not pursue recommended goals and reforms and there will be limited muscle memory when an emergency arises. Even if the group's leadership is motivated and active in the interim period, there is an additional risk that member institutions will prioritize the pursuit of contradictory programs or priorities at the expense of the partnership's cohesion and success. Thus it is critical that leaders of the broader governance structure—whatever form it takes—are imbued with sufficient authority and funding to pursue ambitious programs, and are accountable for meeting goals and timelines.

Such programs, though initiated by a centralized process, should source advice and collaboration from a wide variety of relevant partners; medical systems, federal health centers, research funding agencies, patient advocacy groups, biotechnology start-ups, established pharmaceutical companies, etc. all hold vital insight into these initiatives. To ensure that these partners have clear lines of communication and engagement, it will be beneficial for the government effort to have a transparent leadership and responsibility structure, rather than a decentralized collection of participants.

Innovating to Address Technological Limitations of Existing Infrastructure

This section will address questions relevant to the collection and analysis of data for emergency clinical trials, focusing on the role agencies can play in supporting new technological and methodological frameworks (questions 2i, 1k, 5).

Regardless of the level of buy-in that can be obtained across agencies and private partners, there exist limitations to the United States' current medical research infrastructure that will impede the efficient and effective management of data in an emergency context. To facilitate large-scale, decentralized emergency clinical trials, there must be a push across health and science agencies to support research and development across the data collection, management, and analysis pipeline.

When aiming to advance rapid, light-touch data collection in emergency trial contexts, decentralized or registry-based approaches can offer convenience for patients and

investigators, increased ease of scaling, and improved access to a diverse pool of patients. The feasibility of decentralized data collection at scale has been advanced with recent technological developments (e.g., health apps, electronic patient-reported-outcome tools, code standardization, and wearable devices). But the substantial variability in data quality and interoperability across tools and companies could hamper their widespread adoption. Collaboration across agencies could make decentralization much more feasible at scale. ARPA-H should consider programs to drive down cost and drive up accuracy of wearable devices and medical apps, especially for diverse populations; the ONC should undertake explicit expansion of its guidelines on interoperability into these new technological contexts to facilitate seamless integration for emergency research; and to ensure meaningful change rather than minimal compliance, NIST should institute research programs to study real-world effectiveness of data integration and develop standards for adoption. These recommendations apply equally (or more so) to traditional centralized data collection; indeed, interoperability of electronic health records (EHR) will be especially important in emergency contexts, and should be strongly incentivized through both requirements and real-world evaluations.

Centralized data management resides on the other side of the coin from decentralized data collection. The importance of centralized data systems was highlighted during COVID-19, when the accessibility of the NHS's pared down, country-level medical records data enabled the UK's Recovery Trial. This trial was vital for determining which existing medications were most effective for treating COVID patients and likely saved hundreds of thousands of lives. While the U.S. is unlikely to pass legislation for its own NHS in the coming years, collaboration between government agencies, private medical systems, and health records companies could lead to great strides in the U.S.'s capacity to transfer and store large quantities of simple health information to facilitate research in emergencies. With companies like Verily and Epic already building out their own large-scale trial infrastructures, the NIH and ARPA-H are well-positioned to prioritize ambitious goals for a national (emergency) clinical trial infrastructure. The federal government can also utilize its programs that fund rural and low-capacity hospitals and clinics to build out technical infrastructure needed to reach the most vulnerable populations typically missed by clinical trials held in large urban centers.

Finally, the development and approval of state-of-the-art methods for large-scale data analysis are critical for ensuring that emergency trials can be completed—and learnings can be implemented—as efficiently as possible. The UK's Recovery Trial again provides a strong example of a highly efficient multi-intervention protocol. But in the absence of a centralized health system like the NHS, the U.S. will need to invest heavily in new data analytic approaches to build internal capacity. Here, again, multiple agencies should be coordinated to pursue this effort. The FDA currently engages with innovative trial designs through its Complex Innovative Trial Design Meeting Program (CID Pilot Meeting Program), which makes it easier for companies to pursue novel designs by presenting case studies to the FDA for review and discussion. Since methods tailored to large-scale, collaborative emergency trials are unlikely to be incorporated into company-specific drug trials, the scope of this program should be expanded to allow academic and corporate methodologists to present hypothetical designs that can be pre-approved in principle rather than as part of a specific case study. The European

Medicines Agency conducts similar investigations and provides qualification opinions for analysis procedures. Beyond trial designs, there is a great need for advanced statistical approaches for EHR data analysis; ARPA-H should consider supporting a program focused on efficient pipelines for cleaning, de-identifying, integrating, and analyzing complex EHR datasets while preserving patient privacy and institutional information. EPIC has shown the power of real-world evidence analysis at a massive scale through their COSMOS platform, studying retrospectively critical care questions like effectiveness of COVID-19 treatments. Rapid investigations of clinical care practice in times of emergency and "peacetime" will enable systematic and ongoing audits of the way healthcare is delivered, to ensure the best quality and most equitable care.

Improving Participation Through Community-Engaged Research

This section will address questions relevant to ensuring equity in clinical trials infrastructure, focusing on the potential for "warm-base" sites to ensure distributional equity of clinical research. (questions 2b, 2c, 3a).

To build up "warm-base" research across the country, OSTP should look to blossoming models of regional engagement sparked by the recent growth of infrastructure funding through the American Rescue Plan, Infrastructure Investment and Jobs Act, and CHIPS and Science Act. These place-based economic development policies focus on investing in communities to create thriving entrepreneurial ecosystems and industries. While funded by the federal government, these programs allow for communities to build infrastructure that works for them, versus having to implement a one-size-fits-all model that is likely to not serve communities' needs. Successful clusters will often: proactively develop multi-year strategies, include a diverse array of stakeholders, rely on evidence to form strategies, see federal grants as ways to build capacity, and research peer communities to identify best practices. We can translate these learnings from cluster development to building out warm-base research, noting that federal investment can spur meaningful private-public partnerships between universities, corporations, start-ups, capital providers, and local governments that help clinical research drive benefits for community members and economies. For example, findings from clinical research can be translated into tangible products through private start-ups and companies. Ongoing research into the health problems that impact a community's well being and ability to thrive economically will drive technology, programmatic, and policy solutions that improve individual quality of life, especially for those most marginalized.

To maximize benefits to communities in underserved areas and meet new statutory requirements for diversity in clinical trials, clinical trial sites should involve community members in the planning stages of trial design and implementation. Our understanding of which problems need "solving" are shaped often by those with the most power and influence, rather than those facing the greatest health inequities. This could look like 1) securing letters of intent with community based organizations (CBOs), with regular compensation guaranteed, to engage collaboratively in execution of trial recruitment, with clauses for emergency recruitment, 2) setting up community advisory boards with communities in decision-making roles to steer the broad directions of trial recruitment, and 3) prioritizing hiring community members to develop

their resources and capacity for clinical trial deployment. If warm-base research is established through a federal grant-making process, grantees should be required to report back on these strategies to ensure proper community engagement is being conducted and show how that has shaped the timeline of the project. Finally, community advisory, such as through an advisory board, should also be a part of the larger execution of clinical research infrastructure; patient representatives could become members of the federal governance board.

Further, it must be noted that to increase engagement in clinical research, trial sites will need to be able to provide meaningful compensation for participation. Trial diversity is often hard to achieve because the most underrepresented communities are both economically unable to take the time to participate due to work, childcare barriers, travel barriers as well as hesitant to engage because of historical exploitation of vulnerable communities by the medical research enterprise. Recent research has found that to engage the most underserved communities, compensation on the order of $500 was necessary to increase likelihood to participate in clinical research. While this order of financial compensation may be difficult to institutionalize, especially in an emergency situation where thousands of people will participate, it does speak to the need to offer tangible resources to meet people's needs. Finally, leaders in expanding clinical trial diversity at the Recruitment Innovation Center at Vanderbilt University have found that it is vital to carefully consider the inclusion/exclusion criteria that might bar people from participating, such as if insurance is required or documentation of citizenship needed. Paying for medical care may increase the overall cost of the endeavor, but will make it more broadly accessible to underserved populations that are often also underinsured or uninsured.

Finally, while digital health technologies will be critical to the expansion of trial infrastructure, they should be used with the utmost consideration for data privacy, broadband access, and recognition of potential inequities baked into the data collection tools. Telehealth technologies have been found to share sensitive health information with data brokers, as the Health Insurance Portability and Accountability Act (HIPAA) has not been kept up to date for telehealth. Cybersecurity is vital to ensure trust in the research process, especially for communities that have been historically harmed by medical research. This could look like developing a "Patient Data and Tissue Bill of Rights" to ensure that trials are structured around data protection and issuing regular compliance notices to trial operators to reiterate providers' legal obligations with respect to patient health-data rights. Further, not all communities can access digital technologies due to a lack of access to the internet. Broadband expansion should be considered as a necessity to have decentralized trials infrastructure. Finally, digital health technologies, from apps to wearable devices, have been shown to have embedded biases that can impact the accuracy of collected data. From computer vision technology being less accurate on dark skin, such as for skin cancer recognition, to pulse oximeters overestimating oxygen saturation, these biases can skew data sets for already vulnerable populations, leading inevitably to less effective treatments. Digital health equity principles should be created for tool procurement to ensure all products purchased for clinical trial use are guaranteed to work on the diversity of the American population.

The following case studies highlight a series of strategies to increase diversity amongst study participants and to expand clinical research sites into underserved areas, for both emergency trials and warm-base research efforts:

Partner directly with communities to coordinate research investigations:

1. Healthy Flint Research Coordinating Center (HFRCC): A partnership between community organizations and academic institutions focused on equitable relationships between communities and academia. HFRCC evaluates and must approve all research conducted in Flint, Michigan. HFRCC helps design proposed studies that would align better with community concerns and context and ensures that benefits flow directly back to the community. Health equity is assessed holistically: considering the economic, environmental, behavioral, and physical health of residents. Finally, all work done in Flint is made open access through this organization. From these efforts we learn that communities can play a vital role in defining problems to solve and ensuring the research will be done with equity-in-mind. This will be especially important at "warm-base" research sites that are investigating solutions to chronic diseases, which are most urgently impacting underserved communities.
2. Patient-Led Research Collaborative: Patient-led research initiative for studying the impacts of long COVID on patients and searching out treatments. Using large, patient support groups, they have conducted online surveys to systematically study LC populations and understand the impacts of disease on life, work, and return to health. They have found that most patients continued to experience significant disability that impacted their ability to return to normal life. Their work highlights the need to take LC seriously as a disease, identify meaningful treatments, and design policies that ensure LC patients can financially support themselves as they recover. The patient voice should play a key role in the innovation process, especially understanding the lived experience of managing chronic conditions. While treatments are highly desired, patients also need policies that support their recovery (such as work from home) as well as safety nets (like disability benefits) that ensure they do not fall into poverty due to their conditions. This speaks to the need for "warm-base" research to not just be about testing medical products, but also programmatic, infrastructural, and policy interventions that tackle the social determinants of health
3. Community Partners in Care: Community Partners in Care (CPIC) was a collaborative research project funded by the NIH, which sought to improve depression care in primary care settings through community-engagement. It compared two ways of supporting diverse health and social programs in under-resourced communities to improve their services to depressed clients: 1) technical assistance coupled with culturally competent community outreach and 2) 4-6 month planning process between agencies and community members to fit the depression programs to community needs. They found that community-engaged processes like the 4-6 month planning period were more effective in decreasing homelessness, improving quality of life, increasing physical activity, and decreasing out-patient visits and hospitalizations. Partnering directly with community organizations can help to evaluate new technologies in the real-world setting

and ensure that the technology comes with a culturally-responsive implementation plan. These community organizations should be compensated for their expertise, given their potential to increase diversity in trials.

Leverage community and patient-review on study protocols to increase buy-in:

4. California Institute for Regenerative Medicine's Patient Advisory Infrastructure: Patients hold 12 of 29 slots on the governing council, including the chair and vice chair. This council approves funding of all grants. All 68 clinical advisory panels also require patient advocates. They have found that while there was initial skepticism about what patients could bring to research processes, they have become vital members of the reviewing effort. Patients have ensured that 1) more risky initiatives get funded 2) impact on patients is discussed in research efforts and 3) skepticism of strategies that only consider human physiology but neglect behavior. Patients' experiences living with disease is often left out of the conversation about high-impact health innovation and clinical trials design. Advocacy boards which give patients the power to decide research directions can ensure that voice is mobilized to fund research that will best enhance patient's lives as well as ensure engagement is always ready to ramp up in the event of an emergency.
5. BMJ Patient and Public Partnership Initiative: *The BMJ* has patients and patient advocates influence day-to-day decision making by championing partnerships with patients in healthcare. Their journal includes patient and public review alongside the conventional peer-review process. Patients in their evaluations identify the wider impacts of illness, burdens of treatment, how conditions are self-managed, and whether treatments are practical. They are also critical of statements without strong evidence, as well as statements that disparage patients. Now, *The BMJ* also requires authors to specify how patients were involved in the research process, from question setting to design to implementation to dissemination. Now those involved in this effort are working to expand patient-voices across health-publishing. Patients have a tremendous amount of knowledge about the broader impacts of illness and can ensure that treatments being tested are practical given the burden of managing the disease. Having these fundamental practices as a part of clinical trials / "warm-base" research guidelines will ensure community outreach becomes a part of the research process.

Utilize technologies familiar to patients to expand access to trial participation:

6. Count Me In: A patient-partnered cancer research initiative that empowers patients to share cancer samples, clinical information, and experiences to accelerate the pace at which new discoveries are made. They use online surveys and sample collection kits mailed directly to patients to understand rare cancers. They are working to study large groups of patients across cancer types, treating institutions, ages, and other demographics to represent the full diversity of cancer patients and their experiences, so that developed solutions have a greater impact on everyone. Their work on rare cancers (25% of adult tumors) was published in *Nature Medicine*, where they were able to see

patterns amongst geographically dispersed patient populations. By working to reduce the barriers to participation in research, CMI believes it will be much easier to study rare diseases and enable new discoveries. Understandings of rare diseases are especially limited by data, which can be hard to collect when populations are small and regionally dispersed - thus any “warm-base” research in this area must be decentralized. Through reducing barriers to participation, patients can play an active role in submitting data that can accelerate healthcare discoveries, regardless of where they are located. Further, because regular communication with participants is a major focus, patients feel connected to the larger research agenda, increasing willingness to continue participating.

Issuing Updated Regulatory Guidance for Products Developed Through ECTs

This section will address questions relevant to regulatory guidance on products investigated through emergency clinical trials. (questions 1i, 2e, 6c).

There should be regular and ongoing communication with regulatory bodies from the centralized governing bodies, given the demands for accelerated approvals and emergency use authorizations for products developed through ECTs. There are a series of trade-offs to consider when approving new medical products in times of emergency. For example, the delay in formal vaccine approval until long after widespread adoption increased vaccine hesitancy due to concerns about taking experimental medicines. Further, this speaks to a lack of public awareness about the relationship between the FDA and sponsors when a product is under emergency use authorization (EUA). EUA products still require phase 1-3 trials as well as a post-market evaluation period to ensure products meet standards for safety and efficacy.

The FDA could consider “rolling-reviews” of clinical data as well as real-world data, as was employed in the United Kingdom and European Union, that allow for regulatory agility in times of crisis. In rolling reviews, data is submitted and reviewed as they become available before the full data package is available. This approach will require a closer collaboration and more intense interaction between the sponsor and the FDA, but is beneficial for accelerating regulatory approval as changes can be made to study protocol along the way versus requiring new, costly studies after regulatory consideration. Living evidence, a strategy described further in the next section, could be an effective tool for collecting this data for examination and analysis by regulators to make critical decisions on the efficacy and safety of products and then communicate those decisions out to the broader public. There is still a risk that products authorized under EUAs could be later found to be less effective, but with a more concrete process for regular review of the data the FDA can pull these products rapidly from the market to prevent any risks to population health.

In times of emergency, data submitted to the FDA could be made available for examination by the broader scientific community. Currently, data submitted to the FDA as part of its regulatory-approval process is kept as a trade secret and not released pre-authorization to researchers. Releasing the data via an FDA-invited “peer review” step in the regulation of high-risk technologies, like automated decision-making algorithms, Class III medical devices,

and drugs, will ensure that additional, external rigor is applied to the technologies that could cause the most harm due to potential biases or data gaps.

Finally, given the national impacts of a medical emergency like the COVID-19 pandemic, it is vital for our tools to work when scaled up to the entire U.S. population. This will not only ensure sites engage in Good Clinical Practice for safety of participants, but also carefully consider equity as a key priority in clinical trial designs. This is especially important with the new statutory requirement for diversity action plans for drug clinical trials. While ensuring equity and generalizability of a tool could slow down progress towards an authorized product, it can reduce hesitancy to uptake and adoption once the technology is at scale as well as mitigate adverse events that further drive polarization on medical products like vaccines. For example, the broad exclusion of pregnant people from vaccine clinical trials led to increased hesitancy to get vaccinated because of the lack of evidence, despite retrospective trials later finding that vaccination was safe during pregnancy. 30% of pregnant people have yet to complete their primary series of the vaccine and only 15% of pregnant people have been boosted as of December 2022, according to the CDC. Further, there should be substantial diversity action plans required of clinical trial operators in order to sufficiently power the study to allow for subgroup analysis as well as multi-factor analysis by race and ethnicity, gender, and age. Finally, for algorithms, multi-site analysis is critical, given the differences amongst clinical populations as well as clinical infrastructure. For example, an algorithm developed at a wealthy hospital using the latest medical imaging technology may have images of much different quality than +15 year old equipment at a federally qualified health center. Thus, algorithms could fail to work at scale in the multitude of contexts necessary for national roll-out. Training should focus on best practices for recruiting diverse pools of participants, leveraging the existing capacity of organizations focusing on diversity, equity, and inclusion in clinical trials such as the Multi-Regional Clinical Trials Center and Recruitment Innovation Center. Modalities should include not only webinars, but also site-specific training, where experts (including leaders in CBOs recruiting people for trials) are paid to travel to sites to provide concrete advice and strategies on sponsor's diversity plans.

Investing in Evidence Synthesis, Implementation, and Communications

This section will address questions relevant to outlining best practices for clinical trial design, and speak to the need for "warm-base" research to also test best practices for scaling up interventions, such as communication and distribution strategies. (questions 1g, 3b).

We live in a time of veritable "scientific overload". The number of scientific papers in the world has surged exponentially over the past several decades and millions of newspapers are published every year. This flood of papers has never been as acute as it was during the COVID-19 pandemic, with thousands of papers published every day, of massively varying quality. Making sense of this deluge of research presents a formidable challenge in a non-emergency context. In an emergency, when the knowledge is growing every day and evidence-based decisions need to be made quickly, the typical process of *(i) scouring the literature for relevant findings, (ii) separating out low-quality or fraudulent research, and (iii) synthesizing studies' results into a format that can inform decision-making* is untenable. With

researchers, policymakers, medical practitioners, patients, and stakeholders all desperate for authoritative information, the lack of up-to-date synthesis can be disastrous.

Living Evidence provides a framework for addressing these weaknesses by treating knowledge synthesis as an ongoing rather than static endeavor. By combining (i) established, methodical methods of summarizing science with (ii) continuous workflows and tech-based solutions for information discovery and processing, living evidence approaches yield a high fidelity signal of science. Such approaches are relatively new, but have already proven demonstrably valuable. For instance, living evidence "helped chart a route out" of the worst stages of the COVID-19 pandemic by providing rigorous and up-to-date knowledge synthesis. Resulting products—like this living systematic review and meta-analysis on drug treatments—were enormously valuable for communicating complex and fast-moving science. In recent years, the World Health Organization has launched a large-scale effort to embed living evidence across its whole portfolio, Wellcome is investing in building Living Evidence resources for mental health research, and AHRQ is incorporating living systematic reviews into their workflow. Such efforts illustrate the rapid adoption of this model by major health sector actors; yet widespread support and capacity-building for living evidence in biomedicine and public health remain rare.

As part of the effort to develop infrastructure for emergency clinical trials, OSTP should explore opportunities to embed living evidence—both its ideals and its practitioners—into relevant agencies, and to fund external efforts housed within public health partner institutions. Importantly, the value of living evidence to emergency trials is not limited to communication of trial results and treatment recommendations after the fact. Living databases for knowledge synthesis would be a valuable asset for tracking characteristics of potential trial sites and assessing readiness, monitoring the evidence base for promising devices for decentralized data collection, promoting and advancing best practices for designing efficient clinical trials, and even monitoring emerging biological threats. In all cases, an authoritative source for up-to-date knowledge would provide an invaluable service to both the government and U.S. citizens.

On the topic of improving "warm-base" research, there is a need to think about ways to implement evaluation of new health interventions in a realistic setting (i.e., the clinic, the hospital, at the point of care) on large, representative populations is a necessity for equitable, safe medical technologies. It should be considered as a part of developing an ECTs protocol. It is challenging to know once new technologies are deployed into the clinic how they are being used and if they remain as effective at scale as they do in a randomized controlled trial. Even if a new intervention works for diverse populations, access issues may stand in the way of its broad uptake by populations, as seen during the COVID-19 pandemic with diagnostics and vaccines. Finally, there are many public health problems that cannot be addressed by a single intervention, such as widespread health misinformation and lack of culturally-competent care strategies. Multi-intervention trials are still a nascent area of research, especially as they rely on novel communications strategies alongside new tools and interventions. FAS recommends funding large scale trials of communication, distribution, and implementation strategies for novel health interventions.

Rapid Acceleration of Diagnostics Underserved Populations (RADx-UP) can be seen as a model for creating testbeds for community engagement on communication, distribution, and implementation. RADx-UP was created to address the issue of vulnerable and historically underserved communities not able to access COVID-19 diagnostics. By deploying rapid grants to initiate community-engaged research and directly funding CBOs to increase capacity for COVID-19 testing initiatives, RADxUP advanced communities' abilities to respond to health crises in ways that worked for their populations. RADx-UP found that for people to access these novel technologies: equitable access had to be ensured, culturally responsive communication and messaging needed to be made to patients, and payment reforms needed to be made to support innovative care management. Without these systemic efforts, a new technology will fail to reach everyone, especially in times of need. Another important finding of this initiative was the importance of data strategies to locate disparities, and then search out context-specific ways of mitigating the barriers, such as the use of mobile units in healthcare deserts. RADx-UP shows that equity efforts cannot be reactive, federal agencies must think proactively about how equity is embedded in the planned roll-out of a technology or intervention for public health.

Thank you for providing this opportunity to respond on ways to strengthen American clinical trials infrastructure. If there are any questions about the content of this memo, please direct them to Grace Wickerson (gwickerson@fas.org) and Jordan Dworkin (jdworkin@fas.org).

Sincerely,

Grace Wickerson, Science Policy Fellow
Federation of American Scientists

Jordan Dworkin, Program Lead, Impetus Institute for Metascience
Federation of American Scientists

I read this RFI with great enthusiasm, and I am hopeful that this can be used to generate a much more streamlined process for rolling out clinical trials (with the emphasis on multiple, which is necessary in series) in an emergency situation.

Although I am a clinical researcher, I am answering in my role as Associate Dean for Clinical Research, so representing our Academic Health System. My comments are generally related to "what lessons should we have learned from COVID-19 to make proactive changes".

As a smaller institution, we have a finite number of PIs and staff that are available to drop everything and participate in emergency research. That said, we were an early and very active member of the NIAID-led trials, and were able to mobilize personnel from many different areas in an "all hands on deck" approach. The ONLY reason we were able to do this is because clinical research in other areas slowed greatly, and so extra staff were available. But that is not a realistic way to look into the future emergency trials, as extra staff from other units may not be available. So attention to the "who can do this" at each site, and how they can be supported while being prepared, is paramount to any discussion.

Related to how these trials should be governed, as we are members of multiple trials networks, it was obvious that multiple NIH institutes were competing for the same sites. We had to determine how feasible it was for our site to accept invitations to participate from NIAID, NHLBI, NCATS, and others, and still consider the dozens of requests we had from our industry partners (an important player to bring to the table). Having coordinator at the highest level of NIH, and assuring that all NIH institutes are working together, instead of competing for sites, needs to be a priority. My suggestion would be to use the already in place Trial Innovation Network from NCATS as a hub, but with input from other NIH Institutes.

Finally, the budget for these individual trials (or platforms) need to be developed to mainly support the sites that enroll subjects (as opposed to the usual structure of support for the central site, with the enrolling sites usually losing money on each subject enrolled). The site PI, study staff, and all support staff need to have their time spent on the study fully supported, and not subsidized by the institutions.

These needs to happen, and can be tremendously impactful. Egos, competition, and central site large budgets needs to be put aside, and there likely needs to be some support for the sites "in waiting". Otherwise, we are destined to repeat some of the same mistakes we made with COVID-19.

Hope this is helpful

Neal

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December 12, 2022

Emergencyclinicaltrials@ostp.eop.gov

RE: Docket No. OSTP-2022-0020-0001 Request for Information; Clinical Research Infrastructure and Emergency Clinical Trials

Sir or Madam:

The Advanced Medical Technology Association ("AdvaMed") is pleased to provide comments on the White House Office of Science and Technology Policy (OSTP) and National Security Council's (NSC) request for information (RFI) on clinical research infrastructure and emergency clinical trials.

AdvaMed is the world's largest trade association representing medical device and diagnostics manufacturers. AdvaMed's member companies produce the innovations that are transforming health care through earlier disease detection, less invasive procedures, and more effective treatments. AdvaMed has more than 400 member companies, ranging from the largest to the smallest medical technology innovators and manufacturers. AdvaMed advocates for a legal, regulatory and economic environment that advances global health care by assuring worldwide patient access to the benefits of medical technology. The Association promotes policies that foster the highest ethical standards, rapid product approvals, appropriate reimbursement and access to international markets.

AdvaMed has General comments and responds to select questions below.

GENERAL COMMENTS

AdvaMed supports OSTP's objective of expanding research into underserved communities and increasing diversity among trial participants and clinical trial investigators. We also support the objective of assuring that large-scale trials can be efficiently conducted across a range of institutions to address outbreaks of disease and other emergencies.

Increasing Diversity in Clinical Trials

AdvaMed strongly supports efforts to diversify medical device clinical trials and has several efforts underway to tackle this challenging issue including:

- AdvaMed's health equity initiative to promote inclusion and equity in health care, partnering in education with stakeholders; promoting research equity in the medical device industry, and facilitating access to innovative technologies. As part of this initiative, AdvaMed hosted three Diversity in Clinical Trial Workshops in partnership with Meharry Medical College. See: https://www.advamed.org/issues/principles/health-equity-initiative. As part of this initiative, AdvaMed has developed recommendations on *Approaches to Increasing Diversity in Clinical Research and Addressing Health Inequities.*

- AdvaMed's Take Her Health to Heart (THHTH) initiative in partnership with SCAI-WIN (Society for Cardiovascular Angiography and Interventions- Women in Innovations) intended to increase enrollment and retention of women in cardiovascular clinical trials. This initiative has been underway since 2015. See: https://www.advamed.org/advamed-women-cardio-campaign.

Additionally, many companies have identified diversity in clinical trials as a high priority, are investing significant resources in this effort, and are pursuing a variety of strategies within their own organizations.

Increasing diversity in clinical trials is a shared responsibility requiring shared efforts by key stakeholders. Participation in clinical trials can be impacted by a myriad of factors such as:

- Whether potential human subjects have access to health care,
- Historical abuse that impacts current human subject considerations for participation in clinical trials,
- Lack of awareness of clinical trials by patients and/or health care practitioners,
- Practice patterns and standard of care,
- Patient preferences, and
- Implicit bias by practitioners, among others.

Some of these issues are beyond the capability of any one stakeholder to address – particularly individual medical device companies – and will require a concerted effort. We believe there is a significant role for the federal government to play in helping to remove structural impediments to more diverse clinical trials and to strengthen the clinical trial infrastructure overall. We have a number of recommendations included below in our responses to the RFI questions.

At the height of the COVID-19 crisis, the medical device industry stepped up and played a critical role in responding to the nation's health care needs by:

- Developing hundreds of novel diagnostic tests under emergency use authorizations including molecular diagnostic tests, antigen tests, and serology tests allowing millions of tests to be conducted per day;
- Developing hundreds of devices under emergency use authorizations including blood purification devices, hemodialysis devices, continuous renal replacement therapy, decontamination systems for personal protective equipment, infusion pumps, personal protective equipment, respiratory assist devices, and ventilators; and
- Ramping up manufacturing to produce needed personal protective equipment required by health care workers on the front lines of the pandemic.

The medical device industry will continue to play an important role in potential future public health emergencies.

Responses to Specific RFI Questions

1.a. Descriptions of models that could be used to establish a U.S.-level governance structure for emergency clinical trials. As noted above, one possible approach would be a centralized U.S.-level structure drawing membership from Federal agencies with relevant expertise.

Response: Consistent with the RFI's reference to "warm base" clinical research capacity, to expand the breadth and depth of the current clinical trial infrastructure into diverse and underserved communities, the Department of Health and Human Services (HHS) and other Federal entities can take steps that are beyond the ability and resources of the medical device industry – to develop a network of community-based health care centers, potentially linked with historically black college or university medical programs and/or with urban medical facilities with concentrations of diverse and underserved populations.[1]

This network could include community and other patient or disease specific advocacy groups that are committed to facilitating diversity in clinical trials. These community, patient and disease groups could receive training on the value of diversity in clinical trials, receive

[1] See: Woodcock: Network of Trials in Community Practices Would Yield Better Results; WCG Centerwatch: The Trusted Source for Clinical Trials Information, Feb. 1, 2021;
Janet Woodcock and Francis Collins dish on lessons learned from the pandemic; March 10, 2021; Endpoint News:
https://endpts.com/janet-woodcock-and-francis-collins-dish-on-lessons-learned-from-the-pandemic/; and
Woodcock Pushes for Pragmatic Trials, Community-Based Research; March 22, 2021; Inside Health Policy:
https://insidehealthpolicy.com/daily-news/woodcock-pushes-pragmatic-trials-community-based-research?destination=node/120669.

training on the benefits of participation in clinical trials such as their gold standard care, be alerted to trials seeking subjects, and agree to be a resource to both federal and industry sponsored trials. Former acting FDA Commissioner, Janet Woodcock, has suggested that community-based health care centers could be supported by specialized Clinical Research Organizations (CROs) that could supply the education and expertise to community health care centers to facilitate clinical research.[2] Once such networks are established, they can be utilized both to meet emergency research needs and by medical device and drug sponsors for to conduct routine medical products clinical trials – helping to maintain the "warm base."

1.j. Appropriate ways to structure a data repository and a biorepository for emergency clinical trial data and specimens. As noted above, one potential model would be to collect data and biospecimens in centralized repositories.

Response: OSTP may want to exercise caution in creating a centralized clinical trial data repository. There may be hesitation by human subjects in having their trial data included in a centralized repository that could become a target by foreign or other adversaries, unless strong assurances can be provided that the clinical trial data will be de-identified. Medical device sponsors may also be reluctant to fund clinical trial research if they do not have ready access to the data they collected, and it is housed in a central repository.

With respect to biospecimens that may be housed in a centralized repository, it will be important to enable access to de-identified biospecimens by device sponsors without the current restrictions FDA imposes on industry sponsors which require IRB review and informed consent for secondary use of de-identified biospecimens. Instead, AdvaMed recommends that the Common Rule provision at 45.46.116(b)(9) be applied. The Common Rule language provides clear guidance with respect to research that involves the collection of identifiable private information or identifiable biospecimens.

The Common Rule requires one of the following statements about any research that involves the collection of identifiable private information or identifiable biospecimens:

(i) A statement that identifiers might be removed from the identifiable private information or identifiable biospecimens and that, after such removal, the information or biospecimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from the subject or the legally authorized representative, if this might be a possibility; or

[2] Building on the foundation provided by the National Institutes of Health (NIH) and its preeminent role in conducting and funding health care research and U.S. medical colleges and universities, OSTP may want to consider whether there are potential learnings from the United Kingdom's National Institute for Health Research (NIHR), particularly its role in: investing in research infrastructure; providing research training targeting women and minorities; and its focus on equality, diversity and inclusion across research and systems and bringing clinical research to underserved communities. For more information see https://www.nihr.ac.uk/about-us/what-we-do/ and https://www.nihr.ac.uk/about-us/our-key-priorities/.

(ii) A statement that the subject's information or biospecimens collected as part of the research, even if identifiers are removed, will not be used or distributed for future research studies. (i.e., that identifiers will be removed and the biospecimen could be used in future research without additional informed consent or that the biospecimen will not be used in future research).

In addition, adopting the Common Rule provision will eliminate the potential for confusion by researchers who seek an exempt determination from an IRB under the Common Rule provision.

We suspect that for emergency research, the first Common Rule option would be heavily relied upon in order to conduct follow-up analyses and research.

2.b.ii. Use of decentralized trial design elements, or other innovative approaches such as trials conducted at point of care.

Response: We support decentralized trial or Point of Care (POC) approaches to enhance diversity in trials. Existing tools and approaches can be better leveraged and utilized. For example, providers should have access to and use technological tools to help identify patients who are eligible for participation in a trial relying on electronic health records (EHR) (e.g., through diagnosis data, demographic information, or other trial inclusion/exclusion criteria). The Centers of Medicaid and Medicare Services (CMS), along with the Office of the National Coordinator for Health Information (ONC), should better coordinate and accelerate efforts to ensure that healthcare providers have the necessary technology to support decentralized trials. They can achieve this through: advances in interoperability that ensure providers can automatically identify trials via their EHR systems; policies that encourage the sharing of relevant, standardized data needed for trial participation while protecting patient privacy; and incentives to encourage providers to actively notify patients of trials for which they may be eligible.

2. c. Incentives that can be identified or enhanced to encourage participation in emergency clinical trial research.

Response: The Federal Government can take important steps now to address structural impediments to more diverse trial participation in advance of a public health emergency. These steps can improve diversity in clinical trials within the entire research infrastructure. We propose six solutions below.

Modernize Human Subject Regulations/Guidance Related to Reimbursement, Compensation and Recruitment Incentives

A simple and straightforward incentive to encourage participation in emergency clinical trial research is reimbursement for out-of-pocket expenses incurred by human subjects, compensation for participant time and burdens, and provision of recruitment incentives. However, the HHS guidelines are outdated and are implemented unevenly by Institutional Review Boards (IRBs). In order to increase diversity in clinical trials, we recommend that HHS modernize its human subject regulations and/or related guidance. AdvaMed has previously recommended that guidance on payments to human subjects be updated and modernized to reflect current views citing recommendations made in the *Harvard Catalyst Guidance: Paying Research Participants: Ethical Guidance for IRBs and Investigators* which establishes guidelines for: (1) reimbursement for out-of-pocket expenses incurred by participants, (2) compensation for participant time and burdens, and (3) recruitment incentives without regard for income status. These items are truly associated with participation in the trial rather than becoming a source of income for a participant which may inappropriately affect their decision to participate. In conjunction with this review, HHS could establish a fair market valuation for participation in any clinical trial (perhaps based on degree of risk) to avoid the conundrum that socioeconomic differences will result in different fair market valuations for different human subjects. The goal should rightly be to increase clinical trial diversity and participation by appropriately reimbursing and compensating human subjects, not that participation in trials serve as a source of income for human subjects.

Update Regulation and/or Guidance on Supplementary Investigator Reimbursement

We also recommend HHS update its regulation and guidance to allow for supplementary reimbursement of investigators and investigational sites for the additional time it may take to recruit diverse trial subjects. Currently, reimbursement for these activities may be misconstrued as coercion or undue influence of human subjects.

Establish A Safe Harbor for Financial Assistance vis a vis Anti-Kickback Statute

We also suggest that HHS establish a clearly defined safe harbor as to what types of financial assistance and how much will be considered violations of the federal Anti-Kickback Statute (AKS). Clinical trial sponsors are currently reluctant and unsure whether transfers that could be interpreted as high value (e.g., transportation vouchers, childcare reimbursement, donations of iPads or Apple Watches to facilitate trial participation, hotel stays for patient engagement on clinical trial protocols, supplementary reimbursement of investigators for the additional time associated with recruitment of diverse trial participation, etc.) can be considered violations of the AKS.

Development of Trial Guidance that is Least Burdensome for Human Subjects

HHS should also develop guidance for trial sponsors on trial conduct and trial protocol designs that are least burdensome for human subjects. These could include centralized trial designs, alternative clinical trial follow-up requirements such as: requiring fewer follow-up visits, allowing phone follow-up or home visits by nurse trial coordinators (in lieu of in-person visits by patients/subjects); allowing for on-line follow-up options; permitting the patient's/subject's primary care provider to perform some of the follow-up requirements and to reimburse for such; allowing for weekend hours for required follow-up visits; allowing virtual or telemedicine visits; allowing use of wearable technology to record key health parameters, and use of alternate labs or imaging centers (closer to where human subjects live). Least burdensome human subject clinical trials could significantly help recruitment and retention of diverse human subjects. Although many of these options have been included in guidance issued by FDA and used successfully by sponsors during the pandemic (i.e., *FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency*, March, 2020), the guidance should be expanded to include other alternatives – in addition to those outlined in the guidance – that sponsors may have used and be focused exclusively on acceptable approaches that are *less burdensome for human subjects.*

Coverage of Routine Patient Costs by Medicaid for Device Trials

In order to ensure more racially and ethnically diverse clinical trial participation, Medicaid should cover routine patient costs associated with approved clinical trials. This is a critically important mechanism to support Medicaid beneficiary participation in medical device clinical trials. Indeed, the importance of Medicaid to drug development and helping to diversify participation in clinical trials has been recognized by Congress which passed the Clinical Treatment Act as part of H.R. 133 (Public Law 116-260). The legislation requires state Medicaid programs to cover routine patient costs for items and services that are provided in connection with a qualifying clinical trial in relation to the prevention, detection, or treatment of any serious or life-threatening disease or condition.

Unfortunately, in an apparent oversight, the legislation only covers drug clinical trials and does not cover medical device clinical trials. However, Medicare has a longstanding policy of covering routine patient costs for medical device trials. This oversight should be corrected, and the Clinical Treatment Act should be expanded to include Medicaid coverage of routine costs associated with medical device trials. Ensuring that medical device trials are on a par with drug trials vis-à-vis Medicaid payment of routine costs associated with clinical trials would mirror a long-standing Medicare program for devices.

Better Publicize ClinicalTrials.gov and Make it User Friendly for the General Public

ClinicalTrials.gov was expressly developed to provide more transparency about clinical trials, provide public access to information (both positive and negative) about publicly and

privately supported clinical trials and to help potential subjects identify clinical trials that are actively recruiting patients. However, the current website is complex and not easily navigable by lay users. A lay-user interface should be developed including lay-user clinical trial descriptions to facilitate recruitment. The National Library of Medicine (NLM) should also develop lay summaries of trial results. The existence of this important resource should also be better publicized.

3.c.ii. Whether "warm base" research could be appropriately supported as a public private partnership.

Response: In the event of a new outbreak, we recommend developing public-private partnerships to facilitate the development of products to place into the National Stockpile for high-risk pathogens. In this way, warm base research could support ongoing development of products for the National Stockpile that are within expiration dates. In the event of a public health emergency or disease outbreak, companies – especially *in vitro* diagnostic companies – who may have ongoing studies intended for FDA clearance or approval for a disease that is related to the pathogen that is part of the public health emergency or disease outbreak, could also be encouraged to expand those studies to include the specific pathogen in question.

4.a. Emergency Master Agreement Basic Terms

Response: We agree that in order to incentivize the private sector to participate in emergency medical research, it will be important to ensure confidentiality of industry business information and processes that may be developed in response to outbreaks of disease or other emergencies. Similarly, protection of associated intellectual property or patents developed by the private sector will also need to be assured. This may include limiting clinical trial data access only to the sponsor that developed the data. Since the conduct of clinical trials and the resulting data is the costliest and most resource intensive part of the development process, limiting access to the sponsor that developed the data will be important. Sharing data developed by one sponsor with their competitors is very likely to disincentivize private sector participation.

Thank you for this opportunity to provide input on the RFI. Please don't hesitate to contact me if I can respond to any questions.

Respectfully submitted,

/s/

Tara Federici
Vice President
Technology and Regulatory Affairs

Request for Information: FR Doc. 2022–23110

Office of Science and Technology Policy (OSTP) – Clinical research infrastructure and emergency clinical trials

December 27, 2022

Business Details
Name: BCG Inc.
Type of Stakeholder: Strategy advisor to leading public and private sector healthcare organizations

1. Governance for Emergency Clinical Trials

a. Descriptions of models that could be used to establish a U.S.-level governance structure for emergency clinical trials.

In 2020-1, an unprecedented number of clinical studies were initiated to assess vaccines, therapeutics, procedures, and other interventions against COVID-19. While several effective vaccines and therapeutics were successfully identified and developed, this experience also revealed key shortcomings and yielded considerations for clinical studies in future emergencies.

Here, we first describe requirements that an emergency clinical trials governance structure must meet, next we identify success factors based on learnings from the COVID-19 experience. Starting with the key requirements and success factors helps us constrain the set of potential governance structures for deploying clinical trials capabilities.

I. Requirements for Clinical Trials Governance Structure

At minimum, a governance structure for emergency clinical trials should enable the United States Government (USG) to:

- **Determine which studies to conduct and prioritize in line with the most urgent public health needs.** This would help reduce duplicative studies, allow the Government to pursue a balanced portfolio of efforts, and importantly, support studies that may not be otherwise conducted due to the lack of a commercial motive (e.g. repositioned off-patent medicines, combination therapies).

- **Influence study design**. The model should allow USG to shape essential factors of trial design, including but not limited to the study population, inclusion and exclusion criteria, key endpoints, study size and length, minimum expectations regarding racial/ethnic diversity of trial participants, and the statistical analysis plan. This would help ensure that the studies address the most important clinical questions in the population(s) most impacted by the emergency, that the study is appropriately powered to yield an unambiguous result, and that the evidence from different studies can be reasonably compared.

- **Access a large network of investigators and health care facilities.** The network should ensure the right specialized expertise is available, and that a clinical study can be quickly enrolled with even a small subset of network sites.

- **Reach and enroll study subjects across geographies and demographic groups**. The emergency may be especially concentrated in certain regions, care settings, or in certain population segments, especially those that are typically not well represented in clinical studies (e.g. racial and ethnic minorities).

- **Maintain operational oversight of studies**. In the rapidly evolving context of an emergency, it would be important for USG to actively monitor study execution, so that resources could be deployed where needed (e.g. surge capacity in a community experiencing an outbreak), and any necessary course-corrections can be implemented.

- **Possess first-class access and rights to study data.** This would help ensure that important study findings are disseminated and incorporated into public health decisions quickly, that the full set of analyses are conducted, and that access can be granted to other researchers for addressing a wider set of questions.

II. Key success factors for governance structure

The experience with conducting clinical studies for COVD-19 suggests a few key success factors for the proposed emergency clinical trials governance structure. Such a structure would ideally:

- Be **flexible**. The model should not be constrained to specific pathogens or disease types and should be able to re-size in terms of investigators, sites, subjects, etc.

- Be **robust and have low complexity**. A structure with redundancies for core processes (e.g. subject screening and enrollment, data entry and capture) is more likely to succeed versus a highly efficient, streamlined system with critical points of potential failure.

- Be **low burden** for investigators and sites. Joining and staying within the network, and joining a particular study should be straightforward and require minimal effort.

- **Bias to the fastest route to clinically-relevant, high-quality evidence.** Targeted data should drive public health decisions as opposed to obtaining breadth of evidence.

- **Have a low activation energy and maintain a state of readiness.** Be able to stand up and execute a clinical study quickly without extensive effort and planning

- Have the right balance of **incentives for industry partners.** Encourages collaboration on finding solutions that advance public health while maintaining commercial attractiveness.

- Be able to leverage the breadth and depth of USG resources. Has the right representation from external academic, indsutry and other experts for **scientific independence.**

III. Governance structure options and considerations

While clinical studies can vary markedly by disease area, experimental design, and context, executing any large, modern clinical study is a complex endeavor that must draw upon an essential set of capabilities and resources. Below, we review these capabilities and assess the degree to which each capability cluster is specialized for a particular study, the appropriate unit of resource deployment, whether there may be advantages to pre-deploying or maintaining standing resources, and the appropriate level of control that the governance structure should have over the capability.

Capability / Resource	Considerations for governance structure
<u>Clinical Development</u> • Study design • Study steering • Biostatistics • Medical monitoring, safety / Pharmacovigilance • Regulatory	• Study design depends in large measure on the particular disease and intervention • Important for governance structure to be able to provide input into study design and steering, but preferably via a formal mechanism (not directly) • Most resources not highly specialized • Each study requires its own dedicated resources • No significant advantage in maintaining standing resources
<u>Site and investigator network</u> • Sites and investigators in academic medical centers, community health departments, clinics, dedicated clinical research sites, etc.	• Some specialization – not all sites can conduct every type of study • Highly advantageous to maintain a standing network from which sites can be activated quickly for a new protocol without the typical long lead-time administrative tasks (e.g. IRB, contracting)
<u>Clinical operations</u> • Study Management and Documentation • Site Enablement and Management • Subject Recruitment • Site Monitoring	• Low specialization – large contract research organizations (CROs) are able to execute a diverse array of trials • Each study requires its own dedicated resources • No advantage in maintaining standing resources for all operational capabilities. However, can be

• Business Operations • Training and Compliance	advantageous to establish a framework into which any CRO can be activated when needed
<u>Data and systems</u> • Clinical data systems • Operations systems • Programming and Data Capture • Data interfaces • Data Management	• Low specialization for systems – study-specific data stores can be created on standard data systems infrastructure • Dedicated, study-specific resources needed for some capabilities • Important for governance structure to have a formal mechanism to enable first-class access to data, without relying on third party assent and action
<u>Translational Medicine</u> • Diagnostic assays • Immuno-assays • Sample logistics	• Assays are highly specialized, tailored to specific diseases or interventions • Standardization and alignment on assays greatly facilitates comparisons across interventions • Potential advantage in creating network of leading academic labs and maintaining some level of activity and engagement (e.g., by issuing tasks for work in emerging pathogens)
<u>Supply</u> • Investigational product • Comparator product • Ancillary study supplies	• Investigational product highly specific to study • While not possible or practical to maintain standing resources, a framework to facilitate access to products not commercially available (as investigational or comparator) could be valuable

The above considerations for key capabilities suggest constraints on the space of potential governance structures. Specifically, the core capability clusters can be grouped as follows.

Standing infrastructure that the governance structure should stand up and maintain on an ongoing basis

- *Data and Systems.* A standing clinical data management system operated by USG can enable the desired level of data access, can help establish standards that can further enable the development of interfaces over time to capture data from electronic health records (EHRs) and other sources, and can maintain compliance with the appropriate requirements so that the data can be used in regulatory filings.

Expertise and infrastructure networks that the governance structure should maintain linkages to, with the aim of quickly activating an appropriate subset when the need arises.

- *Site and investigator network*. The focus here is on accelerating (or skipping altogether) the typically time-consuming and iterative administrative steps (e.g., IRB approval, contracting) by maintaining active, formal relationships with the governance structure. Additionally, periodic non-emergency efforts on other diseases (e.g., seasonal influenza) can enable the governnce structure to conduct practice runs while at the same time collect valuable public health data.
- *Assay lab network.* A network of academic labs and traditional central laboratory service providers that can be activated for assay development and testing capacity. Additionally, USG could help maintain active engagement by running yearly challenges to this network to develop assays targeting emerging pathogens.
- *CRO network*. Analagous to the assay lab network, a set of CRO relationships with the appropriate Standard Operating Procedures and connections already in place to enable fast stand up and resourcing of new studies.

Study-specific capabilities and resources which are highly situational, and for which there is no meaningful advantage in pre-positioning. These include *Clinical Development, Clinical Operations, and Translational Medicine.*

Governance model archetypes

We believe that establishing a framework in which capability clusters can be reliably activated, and assembled as modules to enable the fast stand-up and execution of a study is more important than establishing a precise governance structure. Nevertheless from the above considerations, two archetype governance structures begin to emerge.

Both governance structures have the following attributes:

- *Clinical Research Agenda Committee.* This is intended as a joint body of USG agency representatives, external physician scientists, and public health experts that is tasked with reviewing study proposals and prioritizing them for execution.
- *Study / Protocol leadership group.* This body is intended to be stood up once approval for a particular study is given, and would provide the intellectual leadership and steering of the study including study design, oversight, interactions with DSMB, etc.
- *Study execution group*. This body is intended as the operational arm of the Study / Protocol leadership group.

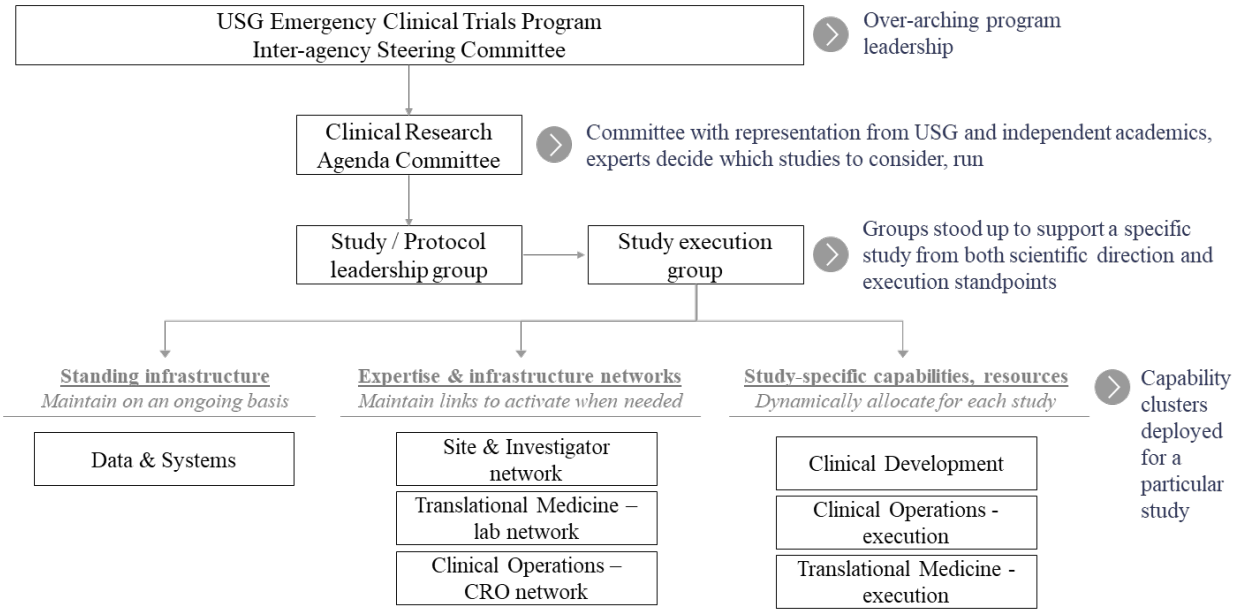


Figure 1. *Depiction of the governance model structure, including key governing bodies and stakeholders (black boxes), roles and responsibilities for each (gray arrows), and distinction of which capabilities should be established (bottom left), in network (bottom middle), or allocated on a study-specific basis (bottom right).*

From the governance structure above, two separate governance models emerge based on which entity is responsible for driving each group or activity.

In **Model 1**, USG drives study execution. In this model, USG would effectively adopt the role a of study sponsor. Specifically, it would drive both the Study/Protcol leadership and Study execution teams. Additionally, USG would contract with a CRO to allocate study execution resources.

In **Model 2**, USG facilitates aspects of study. In this model, USG would still provide the Data and Systems infrastructure, and bring to bear the Expertise and Infrastructure networks; however, a separate sponsor (typically the manufacturer/developer of a new investigational product) would drive the Study Protocol leadership and execution groups, and would likely also deploy its own CRO for study-specific capabilities.

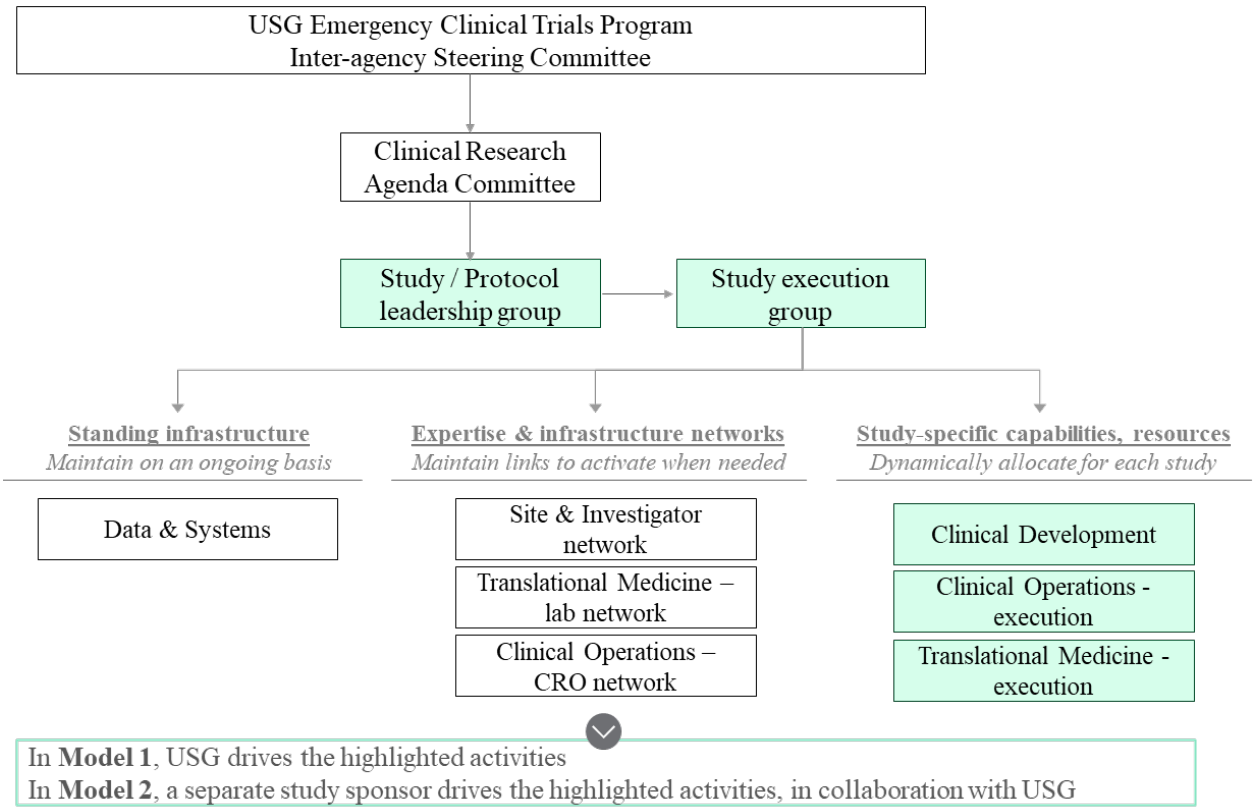


Figure 2. *Depiction of the two governance model archetypes, where the green-highlighted boxes indicate differences. In Model 1, USG would drive green-highlighted groups and activities. In Model 2, these would be driven by a separate, non-government sponsor.*

b. Criteria that should be applied in determining when coordinated and potentially large-scale clinical research is needed to address an outbreak of disease or other biological incident, including signals or indicators that should be taken into account.

The worldwide experience with COVID-19 highlighted the difficult in predicting the trajectory of an outbreak. Despite the biomedical community's knowledge and understanding of Coronaviridae, a clear understanding of the fundamental attributes of the SARS-CoV-2 virus and COVID-19 disease took months to develop. We believe that a low threshold for activating clinical studies can enable collection of valuable data to potentially inform important public health measures. Additionally, it would allow the governance structure to gain practice in quickly standing up and executing studies.

Criteria applied to determine whether emergency clinical studies are warranted should include:

- Whether the disease or incident is poised to spread
- The scale of the potential public health impact
- The extent of understanding of the potential clinical outcomes of the disease / incident
- Whether the available thereapeutic options and other tools are adequate

2. Identifying and Incentivizing Research Institutions and Networks; Building Diversity and Equity

Clinical research has a dismal track record of racial/ethnic minority representation; the enrolled population in most studies is not representative of the racial/ethnic composition of the United States – let alone representative of the burden of the specific disease. This discrepancy to some degree reflects the structural inequities in access to care, and hence can be difficult to overcome in the context of a clinical study.

While a comprehensive, long-term strategy and plan that holistically addresses barriers to racial/ethnic minority inclusion in clinical studies would need to be developed, we have found that two nearer-term practical approaches can meaningfully increase participation: (1) selecting sites in locations with higher proportions (e.g. in terms of US census data) of racial/ethnic minorities, and (2) setting and enforcing clear, numeric expectations on enrollment diversity with sites.

Conclusion

The COVID-19 pandemic highlighted the critical need for data from robustly designed and well-controlled clinical trials that can be unambiguously translated into clinical decision-making. Implementation of a Clinical Research Infrastructure such as the one envisioned in this RFI can greatly accelerate the pace at which therapies and other interventions are assessed, and thereby potentially save many lives and add tremendous public health value.

December 22, 2022

To: Dr. Carrie Wolinetz, OSTP Deputy Director for Health and Life Science and Grail Sipes, Assistant Director for Biomedical Regulatory Policy

We write on behalf of Boston Medical Center, the largest safety-net hospital in New England, to provide input on U.S. capacity for emergency clinical trials. Boston Medical Center is a 514-licensed bed facility with close to 900,000 outpatient visits and 24,000 inpatient admissions in FY21. Our patient population is racially, culturally, and linguistically diverse, as shown in Exhibit I. The top two preferred languages of our Limited English Proficient patients are Spanish at 49% and Haitian Creole at 15%. Boston Medical Center's mission is to provide Exceptional Care, without Exception.

Exhibit I: BMC Patient Population

We are very interested in learning more about OSTPs vision for a future clinical trial network that can rapidly implement state-of-the-science trial designs in response to national emergencies and future health threats. **We urge strongly, however, that OSTP include in its focus on expediency an equal commitment to equity in execution**. We share our perspective, which we forged during the early COVID-19 pandemic, and provide concrete actions that OSTP can take to ensure that the science of the future is diverse, equitable, and inclusive.

In March 2020, the COVID-19 pandemic reached New England. Boston Medical Center was beginning to fill with COVID-19 patients, and ultimately 72% of the 6,288 admissions were among Hispanic/Latinx and Black/African-American patients. See Exhibit II for further demographic breakdown of COVID-19 admissions from 2020-2022. The hospital reached 100% of its surge capacity and at that time, Boston Medical Center had no clinical trials of SARS CoV-2 therapeutics available for its patients, despite the fact that we are an experienced clinical research program with over 250 active clinical studies across the full spectrum of 21st century medicine and ranked 18th in direct NIH funding for independent hospitals. Notably, our research portfolio had included clinical trials of anti-viral therapeutics and immune modulating therapies with several of the sponsors of early SARS-CoV-2 trials. We applied to be a site for COVID-19 trials, we were not selected or even evaluated as a potential site. At the same time, the Infectious Diseases Society of America released its first guidance for COVID-19 therapeutics, which identified seven candidate therapies and indicated that none were appropriate for use outside of a randomized controlled trial. Thus, Boston Medical Center, and

Exhibit II: All BMC COVID discharges

Black	42.9%
White	20.3%
Hispanic	29.1%
Unknown/Declined	4.7%
Asian	3.1%

hundreds of other essential hospitals around the U.S., were instructed to standby and await instruction from our better connected and well-resourced colleagues at established research centers. While we waited, our diverse patients and community were unable to participate in the rapidly expanding accumulation of data to gather insight into the scientific understanding of this disease.

We advocated with the sponsors of clinical trials to understand why we were overlooked in site selection and how we could bring opportunities to our community. A candid call with leaders of one of the major manufacturers of early SARS CoV-2 candidate therapies cast light on the structural barriers we faced. It was clear that the world was experiencing a global viral event, and it was also clear that they needed to open emergency clinical trials in the U.S. and Europe, immediately and on a timeline that they had never done before. Expediency was paramount and became the sole guiding principle to all decision-making.

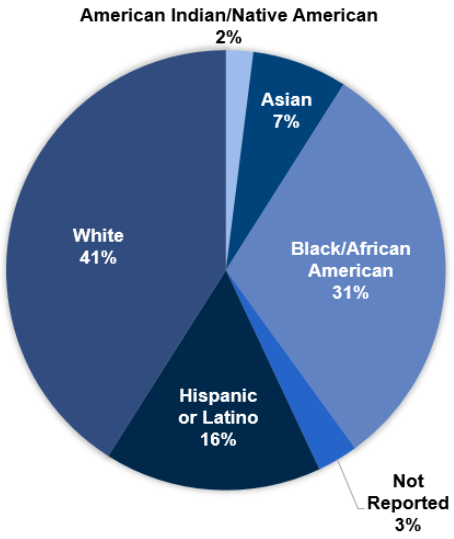
With the first priority being speed, the optimal approach was to contact established investigators with pre-existing clinical trial experience and the flexibility to re-purpose resources that could support their existing infrastructure and enrollment experience to execute emergency SARS CoV-2 trials. But while the intention was clear and understandable, the unintended consequence was that site selection largely excluded hospitals that were caring for communities of color most directly and disproportionately impacted by COVID. This exclusion further led to inequitable access to potentially life-saving investigational therapy, as well as suboptimal diversity in enrollment in these trials. The disparity was alarming, with some hospitals having multiple clinical trials of compounds in the same drug class, while others were told to wait for data.

The result of that call was a remarkable change in the pharmaceutical manufacturers' approach to site selection. With an understanding of our patient population and the research capabilities that were available at Boston Medical Center, first one, and then many sponsors came back to Boston Medical Center, asking if we could participate in their trials. Working with the Boston University Clinical Translational Science Institute, Boston Medical Center rapidly developed and deployed clinical trial capacity, during the height of the first wave of the COVID pandemic. In Spring 2020, we enrolled our first participant in a COVID interventional study for an immune modulatory therapy in severe/critical COVID-19. The first participant that we enrolled was born outside of the United States and Limited English Proficient. Our participant was the first non-primary language English speaker to enroll in the study nation-wide.

Between April 2020 – June 2021 we activated or completed 25 COVID-19 clinical research protocols and enrolled 3,000 participants. Collaborating with Boston area hospitals and universities we established one of the first SARS-CoV-2 bio-specimen repositories, and published that process in the Annals of Internal Medicine. We became a site for the NCATS-sponsored ACTIV network and the RECOVER COVID Initiative. We are proud to report that our

Principal Investigators and study team members worked tirelessly to enroll 61 participants across the 6 ACTIV trials with a demographic breakdown, as shown in Exhibit III and to date have enrolled 96 participants in the RECOVER COVID Initiative. Additionally, our extraordinary Pediatric research team enrolled 236 participants within 8-weeks for the Pfizer vaccine trial and subsequently expanded opportunities for our patients by opening enrollment in the pediatric vaccine trials and adult/pediatric booster trials.

Exhibit III: ACTIV Network Enrollment Demographics



We also designed a workforce development program to train a new generation of culturally sensitive, racially, ethnically, and linguistically diverse research staff, and became a member of the NHLBI CEAL network. Boston Medical Center is now working with philanthropic donors, the NIH, and the City of Boston to fund and expand our model of conducting community-engaged and inclusive research in a safety-net hospital setting. We published our experiences establishing the infrastructure and working with the community in the Annals of Internal Medicine.

We learned many lessons along the way. The following are lessons that we feel are important to share as OSTP forms vision for the future of clinical trials in America:

1. **Driving for expediency, without intentionally focusing on equity, compromises the ability to engage diverse patient populations and prevents necessary community-engaged trust building.** Expediting research enrollment, without community engaged trust-building partnerships, leads to expensive, wasteful, and predictable consequences. Rapid trials that do not represent the U.S. population are not generalizable and may require repetition. It is worth investing resources up front, agnostic to specific trials, to ensure that research is inclusive, equitable, and community engaged. One critical step in achieving equitable science is building trustworthy relationships within the local community in advance of specific research enrollment opportunities. General research awareness that is not tied to specific trial enrollment or medical focus encourages open dialog with a respectful timeline.

   While it is not easy to build trust and infrastructure that encourages diverse populations to enroll in research, we have developed an intentional commitment to health equity, even if sometimes that means small compromises in speed. Boston Medical Center leadership saw this opportunity and invested in a new model that brings together community engaged values and infrastructure, with the rapid activation and oversight of strategically important, under-resourced clinical trials; first with the important ACTIV Network trials, then expansion into pediatric Paxlovid, and a future pipeline based on a

population health needs assessments. The **Clinical Research Network** is Boston Medical Center's answer to building a research program worthy of trust and leads community engagement initiatives both broadly and as an additive educational and training approach to culturally sensitive study specific recruitment practices. A call to sustain and grow the Clinical Research Network is imperative to share with other lean organizations that a model built around inclusive clinical research practices can be efficient, engaged, and successful.

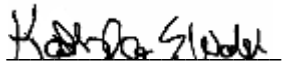
2. **Achieving equity in trial enrollment requires investment.** When we first began working with sponsors, we ran into budgeting challenges when we asked for funds to support multi-lingual translations of materials and long, complex enrollment processes. We therefore analyzed our screening logs, to provide the business case for our budget requests. We learned that we approach approximately 12 potential participants to enroll 1. Many of those interactions are across cultures and languages and require hours of dedicated person time. Often, we work with eligible participants for 2-4 hours before they ultimately decide to decline study participation. Quite simply, it costs more to enroll a diverse clinical trial cohort. It should not come as a surprise that improving the current system will require resources to support more inclusive engagement. For example, we recognized that a research participation letter to an employer may prevent a participant from losing their job, but that the study compensation may not cover their lost hourly wages and the negative financial consequences prevent enrollment. Therefore, to facilitate equitable participation, we created alternative research follow-up visits outside the standard 9-5 clinic schedule and secure additional funding to support transportation costs.

3. **Prioritize equitable funding, not equal funding, between sites**. Beyond investment, attaining equity requires intentionality in building budgets. When we began working with sponsors, we frequently heard that other sites did not have the same costs as Boston Medical Center and it would not be fair to budget more money to Boston Medical Center for the same work. However, safety-net sites like Boston Medical Center are not doing the same work as traditional, university-based clinical research sites. We approach 12 patients to enroll 1, whereas other sites in Boston approach 2-3 patients to enroll one. Most of our interactions are in languages other than English, requiring interpreter services and multiple hours of communication – which most often ends with a decision to not participate in the study. Further, when the work is done, safety-net hospitals deliver diverse enrollment that many traditional sites cannot achieve. Historically, the number of participants enrolled was the bottom-line currency of trial implementation and a measure of success. In the vision we share with you, the demographic and linguistic diversity of enrollment will be an equal consideration and something that merits investment. Further, such progressive budgets and the process of budgeting itself, could financially modeling engagement practices that attain equitable enrollment.

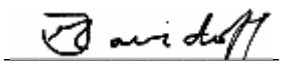
4. **Be thoughtful about balancing cutting-edge, adaptive trial designs with the need to provide truly informed consent across cultures and languages**. We appreciate the need for adaptive and efficient comparative effectiveness designs. Indeed, the experience with overlapping and even competing trials during the peak pandemic is one of the main motivators of this call for perspectives. At the same time, informed consent is extremely challenging – even with a traditional arm A vs arm B single randomized design. As part of our work leading the Massachusetts Community Engaged Alliance of the NIH (MA-CEAL), we analyzed qualitative interviews from 50 people of color who were participants in a clinical research study. Nearly every participant wanted to discuss challenges with informed consent and confusion about the protocol. Participants reported that they could not understand the study design and were not clear of the schedule of events. Transferring comprehensive knowledge about the many possible twists and turns of an adaptive trial design will be very challenging. To be clear, we agree that it is essential that we begin to implement more efficient and adaptive trial designs to reach our research goals, but that movement comes with a potential cost in terms of accessibility. It is critical, therefore, that we couple the movement toward innovative adaptive trial designs with equally innovative research investigating how to communicate those designs across cultures and languages and how to ensure truly informed consent. The workforce development program that we are building at BMC is one of the highest priorities for our clinical research strategic plan. A clinical research workforce development program with a diverse pipeline of enrollees from the community could support trust building, encourage economic mobility, and improve research awareness and engagement to ultimately advance science with and for all people.

We appreciate the opportunity to provide comment and are excited by OSTP's vision. Going forward, we urge OSTP to balance its focus on efficient design and rapid deployment with an equal commitment to equity. We at Boston Medical Center have lived the experience and seen the structural biases that emerge when trials focus solely on implementation speed. We are confident that the innovative clinical trial network of the future can harmonize expediency and equity to have the kind of deep impact that we all envision for the future of science.

Sincerely,



Kate Walsh, Chief Executive Officer



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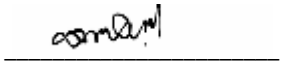
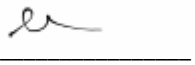
Executive Medical Director; Associate Dean of Clinical Affairs



David Center, MD Associate Provost for Translational Clinical Research; Chief Pulmonary



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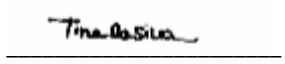

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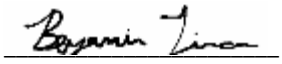
Executive Director, Research Operations



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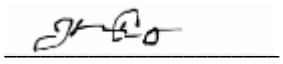
Medical Director Clinical Research Network, PI Massachusetts CEAL



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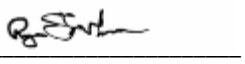
Senior Director Clinical Trial Office, Research Operations



Ryan Schroeder
Director, Clinical Research Network, Clinical Trial Office

Response from Care Access to Support the Request for Information (RFI) on Clinical Research Infrastructure and Emergency Clinical Trials

27 December 2022

Purpose

This document outlines how Care Access Research ("Care Access") can provide clinical research infrastructure for the purposes of supporting large-scale clinical trials that can be efficiently carried out across a range of institutions and sites to address outbreaks of disease and other emergencies.

Contents

Section 1. Company and Capability Overview.

Care Access is a clinical research company that owns and operates a network of over 300 fully integrated clinical research sites as well as a suite of decentralized capabilities that allow us to perform clinical research activities in a variety of settings. We have conducted over 400 research studies and recently enrolled ~1100 racially diverse patients in 6 months in one trial alone. In 2022, we enrolled over 7,000 patients through an established capability that brings any phase 2/phase 3 study to new-to-research, racially diverse communities. Our Decentralized capabilities allow us to access patients in non-traditional locations, either online (virtual) or in person. These combined capabilities include:

- Over 300 fully supported “Brick and Mortar” clinical research sites with diverse populations, with 31 sites having >50% racially diverse patient populations. 57% of Care Access PIs and a majority patient-facing staff are racially diverse.
- Mobile vehicles and trailers that are equipped to perform clinical research activities such as patient outreach and education, pre-screening and screening activities, and clinical research visits
- Virtual Principle Investigators that can oversee research activities and monitor patient safety remotely across multiple locations
- A network of over 1000 contracted physicians that allows access to patients and space to perform clinical visit activities with traveling research staff
- Mobile and traveling research staff that are trained clinical research professionals that travel to the patient to conduct the study visit. The traveling research team can include roles such as Sub-Is, Patient Educators, Study Nurses, Investigational product managers, IP administrators, and Clinical Coordinators. Patient visits can occur in a variety of locations including (but not limited to): Patient’s homes, mobile clinics, temporary clinic locations, physicians clinics, and established clinical research hubs.
- Care Access has a team designed to create and implement operational SOPs and training programs according to regulations and guidelines. These SOPs and training programs create consistent quality across all modes and methodology of clinical research conduct.

Section 2. Governance Model

Components of a governance model that can effectively operationalize any emergency response:

- Collaborative development of clinical trial protocols can be enhanced by site-side ***simulations*** to develop feedback on operational complexity, quality risks, patient experience, and ability to operate at scale. This would include virtual and in-person process mapping, hands on walk-throughs and role playing in order to work through operational complexities.
- Customized Training and Simulations Programs to provide rigorous research training for staff across all experience levels.
- Unique approaches to Project Staffing to help ensure quality, such as building staffing redundancy into deployment systems to ensure that each role has a backup. We also have developed a Study Management Team that can interface with trial Monitors, research staff, and sites to ensure any issues identified internally or externally are tracked, actioned, and resolved. Remote Data Monitoring Teams can augment the monitoring work a sponsor is already doing to ensure data quality.
- Dedicated Remote PI Oversight processes to ensure effective Oversight of remotely conducted Trial Activities. Care Access creates a PI Oversight plan whether we are Principal Investigators ourselves or just supporting PIs at other, non-Care Access sites.

Best practices for designing trials that can enroll vulnerable populations as needed in particular circumstances include:

- Minimizing the length of a visit, specifically the time that the participant is needed on site.
- Allowing for virtual visits, or the splitting of long visits into two or more shorter visits or a combination of virtual and in-person visits. This will allow families to better accommodate the time commitment of trial participation.
- Providing additional on-site space for consenting and visit procedures for pediatric participants who are accompanied by parents, as well as participants who are culturally inclined to attend visits as a family unit and not as an individual.

Technology for projecting and tracking enrollment at study sites, monitoring the progress of clinical trials, and data management should be used.

- Reify Health is the parent company of Care Access. Reify Health's technology called StudyTeam provides a workflow tool for sites to

organize and track their enrollment progress, and it provides real-time deidentified dashboarding of enrollment progress across the entire study for study sponsors. This tool is used by 3000+ sites in the US and 3300+ sites internationally, as well as many of the top pharmaceutical companies. Unlike an IRT system, the StudyTeam platform provides forward visibility into what participant visits are upcoming and scheduled, as well as provide study- and site-level metrics on the source of patients and the effectiveness of outreach campaigns.

- The StudyTeam platform includes an eSource module that can be configured centrally and made available to all sites working on the study, thus expediting site-level activation and increasing overall quality through real-time QC capabilities.
    - **https://www.onestudyteam.com/**

Clinical research sites are accustomed to receiving pre-packaged lab kits and specimen collection materials as part of their involvement in a research study. During the COVID-19 pandemic, the availability of lab supplies was not necessarily a bottleneck, but the ability to package and create visit-level lab kits was a bottleneck. It is important for site organizations to maintain some baseline and, when needed, surge capacity to receive lab supplies in bulk and to then assemble and distribute lab kit packages to site locations on the study. Care Access maintains this capacity to support both Care Access and non-Care Access sites when needed.

Section 3: Identifying and Incentivizing Research Institutions and Networks

Research institutions should be identified by conducting a thorough review of patient databases to confirm availability of patients who have been diagnosed with the appropriate condition of interest or who meet entry criteria. Conducting thorough chart reviews, performing virtual patient outreach, leveraging digital recruiting channels, and performing in-person, on-site screening events to identify patients for enrollment are a few of the mechanisms to identify qualified patients for inclusion.

There are a finite number of research sites in the US, and they vary in speciality and access to particular types of patients. At the onset of the COVID-19 pandemic, Care Access launched the COVID-19 Clinical Trials Alliance to assemble a list of sites that were ready to function during the peak of the pandemic. Existing sites known to Care Access were contacted, as were sites

that users of a variety of site-side technology providers (with a total reach of 3000+ sites). Sites that were capable of operations during the pandemic were then presented to sponsors who were running COVID studies, and many of these sites became top performers. Several key learnings were obtained during this process, including:

- Not every clinical research site will be able to operate during a pandemic. Key factors that determine this include the availability of willing staff, the severity of the pandemic's impact on specific geographic areas, and access to pandemic-specific sanitation guidance and SOPs.
- Large academic medical centers will typically be most burdened by non-trial activities and will have limited in-house resources to allocate to trials.
- The parts of the healthcare infrastructure that interacts with impacted patients are not necessarily connected with active and willing research sites. The research sites that were able to contribute the most to trial enrollment did so through partnerships with networks of Urgent Care and Primary Care facilities that do not have the infrastructure or capability to run trials.
- The sites that were capable of operations throughout the pandemic were in high demand and benefited greatly from staff augmentation services that provided surge capacity traveling or local staff, where available.

Care Access is a leader in bringing clinical research opportunities to underrepresented and often-forgotten communities. A few examples of Care Access' efforts include:

1. Bringing COVID Antibody Treatment study to long-term care facilities across the US. https://www.careaccess.com/about/news/2020/10/1/care-access-research-partners-on-revolutionary-mobile-clinical-trial-for-covid-19-treatment
2. Empowering underserved communities to participate in clinical trials by activating community-based outreach and establishing new sites with new-to-research divers investigators: https://www.careaccess.com/about/news/2021/9/28/care-access-and-eli-lilly-and-company-partner-to-increase-diversity-within-oncology-clinical-trials
3. Establishing community-based research sites across the US to reach new participant populations, such as: https://www.careaccess.com/about/news/2021/11/11/care-access-brings-world-class-alzheimers-research-to-west-central-florida

4. Conducting centrally-coordinated, large-scale studies in regions with no pre-existing research infrastructure by utilizing mobile research infrastructure, traveling staff, and virtual investigators: https://www.careaccess.com/about/news/2022/11/17/first-possible-lyme-vaccine-in-more-than-two-decades

Care Access sites conduct research using two models:

1. The traditional research site model where research infrastructure is integrated into an existing clinic or medical facility. The local practice provides the Principal Investigator and Care Access provides the staff, dedicated equipment, site SOPs, and back-office infrastructure such as financial management, insurance, business development opportunities, and regulatory support.
2. Community-based decentralized research site model relying on two factors:
    a. Community engagement to drive clinical trial recruitment through five layers of engagement and outreach, including (1) Digital patient outreach, (2) Physical presence in the community, (3) Partnerships with local clinics, healthcare providers, and pharmacies, (4) Partnerships with community centers and non-healthcare institutions, and (5) Partnerships with known and trusted leaders in the community
    b. Trial delivery infrastructure custom-built for a local community based on specific needs that determine the location of a site, the Operating Model (e.g. imbedded in a clinic, community center, or stand alone), hours of operation, staff able to connect with the local community culture and language, and operational considerations such as consent language, data and specimen management vetted by local customs and regulations

Operationalizing the local community model relies on the following:

1. Highly experienced Research Staff who can travel to new-to-research site locations and enable and equip local medical personnel to become trained and experienced in research.
2. Principal Investigators:
    a. Highly-experienced virtual PIs that can provide oversight to any active locations on a study.
    b. Comprehensive and time-tested PI training and mentorship program to help local physicians become new investigators.
3. Research Infrastructure:

   a. Research-equipped mobile units that can serve as pop-up research sites and are fully equipped for conducting a wide range of medical procedures.
   b. Ability to rapidly setup a fully-equipped new research site inside of an existing medical facility or community-based setting.
4. Centralized support: Centralized regulatory, source, patient recruitment, data management, QA, and financial management support that can enable any location to infrastructure-enabled and staffed location to function as a research site.

Section 4: "Warm Base" Research

Operationalizing "Warm Base" clinical research opportunities with large community appeal and relevance relies on:

- The introduction of research to a new-to-research community is significantly accelerated when it is coupled with trial opportunities that are particularly relevant for the community. The specific medical indication of interest will vary from community to community.
- Care Access has seen tremendous demand from rural communities in the New England area around a Lyme Disease vaccine study that is particularly relevant for that community. In south-west Louisiana, there has been significant and well-above-average interest in studies involving Obesity, Diabetes, and Cardiovascular studies. In Florida, there has been a particularly high level of interest in Alzhiemer's screening and prevention studies.
- Overall, "warm base" protocols which target wide-spread health conditions and which include an element of early diagnosis and/or health screening are particularly powerful at sparking community-based interest in clinical research. Once activated, a community then has the foundational level of activation and communication channels to support trial enrollment for harder-to-find or rare patient populations.

Section 5: Emergency Master Agreement

Care Access can significantly streamline the contracting and activation of clinical research sites by enabling a single contract to be used for the activation of all sites on a study. Sponsors typically contract to work with Care Access on a particular study across multiple PIs/Sites, and then all participating locations activate centrally using the same Care Access contracted terms and language. This arrangement relies on existing agreements between Care Access and site locations (whether existing sites or new-to-research locations) that can be established in advance of the start of any specific study.

Section 6. Conclusion

In summary, Care Access believes we can contribute significantly to the Emergency Clinical Trials Infrastructure. By engaging our Research Network and Patient Access Locations, and by providing patients with a decentralized option for enrollment and execution, we are able to reach patients that would not otherwise have been able to access or participate in research during emergency situations.

Section 7. Contact Information

Please direct questions related to this RFI to:

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Mobile: +1.317.308.8732

Datacubed Health

Response to: Emergency Clinical Trials RFI

Sponsor: U.S. Government Office of Science and Technology Policy (OSTP)

Date: December 23rd, 2022

Brett Kleger
Chief Executive Officer
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Version 1

EXECUTIVE SUMMARY

Datacubed Health ('Datacubed') is a pioneering patient engagement and data collection company designed for decentralized and hybrid clinical trials. Datacubed's mobile technology platform combines behavioral science with a SaaS technology that can be deployed in hours and is designed to optimize and simplify clinical trial participants experience and adherence.

Datacubed's mission is to ***Advance Health Access to Everyone, Everywhere***. This aligns directly with the goals of the RFI issued by the OSTP, specifically …

- **Diversity, underserved communities** – the patient facing app is deployed via mobile devices. The trial is essentially brought to the patient, so they are not required to visit offices, take time off from work, or be otherwise inconvenienced. If a patient does not have a smart phone, Datacubed provides a device to the patient. The application also does not require a consistent Internet or Wifi access, as it may be used offline.
- **Emergency usage –** most technology providers in the industry require custom-coded solutions that take weeks or months to deploy. In contrast, Datacubed's solution is designed as a multi-tenant solution with an intuitive and flexible administrative interface that allows a study to be set up in minutes or hours, allowing for immediate deployment in the case of emergency usage/outbreaks.
- **Outbreak signals and indicators –** unique to Datacubed, the app includes geofencing capabilities to identify when individuals have entered a medical facility. This has been deployed on vaccine studies to signal when a patient enters a facility, followed by confirmation text with the patient. In an outbreak, this may be configured to signal when a patient enters a facility followed by confirmatory questions.
- **Large scale application -** Datacubed's solution can handle unlimited users and has proven scalability for 10s of thousands of patients, if not more. Combining a state-of-the-art technology infrastructure with the scale of Amazon Web Services (AWS) provides the scale and reliability required for widespread emergency usage.
- **Regulatory –** data collected by the Datacubed platform is regularly used in FDA or EMA submissions for clinical product approvals. Thus, Datacubed is well versed in regulatory requirements.

We welcome the opportunity to assist the OSTP and any partners in this important initiative and thank you for the opportunity to respond.

Brett Kleger

Brett Kleger
Chief Executive Officer
Datacubed Health
Brett.kleger@datacubed.com

OSTP TOPICS

From the topics listed in the RFI by OSTP, Datacubed is responding to the following …

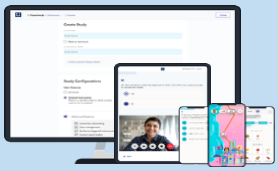
(1) ***Part 2b of the RFI:*** **Effective ways to increase diversity among study participants and investigators, and to expand clinical research sites into underserved areas**.

ii. Use of decentralized clinical trial (DCT) design elements, or other innovative approaches such as trials conducted at the point of care.

iii. Use of technological innovations, such as digital health technologies (DHTs), that would allow remote participation of otherwise limit the need for participants to travel

(2) **Part 5 of the RFI: Identifying viable technical strategies for data capture; gathering information about a potential data capture pilot.**

DATACUBED'S RECOMMENDATIONS FOR ENGAGING PATIENTS REMOTELY:



PATIENT DATA COLLECTION

Patient access via mobile (iOS or Android) and/or web access; includes surveys (all question types), eDiaries, instruments, tasks, and caregiver access. Site focused browser-based experience (tablet and/or web) for collection of patient data.

PATIENT ENGAGEMENT

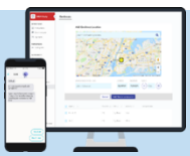
Using a combination of motivational design and behavioral science, the platform features motivators, communications, and rewards intentionally designed to encourage adoption, engagement and use of our app.

TELEHEALTH/ VIRTUAL VISIT

FDA-compliant telehealth available to the staff to videoconference with participants. Offers in-app scheduling and reminders for patients. Offers audit trails and HIPAA- and GDPR- compliant recordings for sites.

ECONSENT

This module allows delivery of predefined informed consent forms (ICFs), capture of signatures, and the delivery of comprehension questionnaires. Signatures are fully FDA 21 CFR part 11 compliant.



GEOFENCING

Location services enabled geofencing around specific areas (e.g. hospitals) to detect health events and case alerts upon fence breaches.

INSIGHTS

Real-time reporting for oversight on the progress of studies. Includes standard insights for instrument compliance, patient demographics and questionnaire detail, and custom insights around eligibility and scoring.

Specific for the emergency use, widescale studies is geofencing. This is a location-based site trigger for alerts when a participant visits a clinic, physician or hospital (optional). It creates a frictionless way to capture adverse event data – no calling patients, no manual data entry, and no data checking. By deploying a virtual fence around a specific location, you can remotely monitor your patients and detect adverse events faster. Additionally, you can automate surveys or questionnaires to be deployed when a participant crosses a virtual fence.

The site burden can be reduced by enabling Investigators to automatically send patients paperwork once they cross the virtual fencing. Upon arrival, participants will receive an alert to complete forms, surveys, or other validated instruments that site investigators must complete in advance of the patient visit. In case of unforeseen visits, remote study monitors can capture that data in real-time, keeping your study on track and your patients safe.

Additional relevant trial data optionally available via a participant's mobile device such as battery usage, steps taken, screen time, apps installed and location. Datacubed Health's platform was specifically designed to engage patients and promote interaction continuously. Users can capture data in person or virtually, allowing you to meet patient expectations. The tools included in our platform are purpose-built to significantly reduce friction and frustration.

Other considerations for the deployment and management of emergency trials include …

- **Integrations** – while integration with other systems might be valuable to exchange data or simplify workflow, each of the modules on the Datacubed platform are native to the application and thus do not require APIs or other integrations. This is critical for emergency usage as it will increase speed to launch, and this is differentiated versus most other technology providers. That said, data integrations may be beneficial depending on the trial design and Datacubed can support them via restful APIs or other methods.
- **Languages –** application is available in any language necessary, and the app itself already includes over 100 languages. For US studies, most often US English and US Spanish are provided, but others are available as needed. If there is study specific content that requires translations, Datacubed manages that via our partners, Transperfect, and can quickly deploy any other languages required.
- **Devices** – if any trial participants do not have their own smart phone, or would prefer not to use it, Datacubed partners with a global logistics supplier (Stefanini) to provision devices rapidly.
- **Content** – often, patients in a study simply require information about the study, progress, or other materials to keep them engaged and informed. Datacubed's app is used to provide this

information, and motivate patients as needed. Datacubed can produce the content internally, via partners, or simply distribute any content produced by OSTP.

- **Training** – for patients, the app is intuitive and includes in app training so that once an account is set up a patient can use it just like any other app on their phone. For OSTP or sites, virtual training is provided typically via web and is interactive, along with full documentation. In person training is always available at a client/site's facility as desired, though for emergency use it is recommended to focus on virtual.
- **Project Management and Behavioral Science support** – included with the Datacubed solution is a project management and behavioral science team who are dedicated to the success of each program. That includes setting up the studies, regular meetings with all stakeholders, analysis of data, and recommendations to improve the program throughout the study. It is not a 'set it and forget it', but rather a team dedicated to manage, monitor and recommend improvements throughout.
- **Help Desk** – a global help desk may be included, 24/7 with multiple language support to handle requests via phone or email as desired.

Thank you again for the opportunity, and we look forward to exploring how Datacubed may help OSTP.

I am submitting this at the public request of Dr Robert Califf, who expressed a strong interest in hearing from clinical trialists.

My name is Eric Lenze. I am Professor and Chair of Psychiatry at Washington University School of Medicine in St Louis, MO. For more than 20 years I have been a clinical trialist, because high-quality clinical trials save lives and improve health. They accomplish this both by showing that new treatments are helpful, and determining that potential treatments are unhelpful and should not be utilized. Both of these have occurred in the COVID-19 pandemic, due to clinical trial results, and as a result, by the fall of 2020 new COVID-19 patients were getting more effective care than COVID-19 patients had received in the spring of 2020.

In the US, by March 2020, it was clear that COVID-19 was a major public health problem, possibly the largest and most urgent in our generation. Moreover, there was no proven treatment for it. Both policy-makers and medical researchers were proposing drug repurposing efforts to mitigate the negative effects of the illness. One good example of this is remdesivir, an anti-viral originally created to treat hepatitis C. There were, and still are, hundreds of potential candidates.

When my colleague Angela Reiersen, M.D., approached me about an idea to repurpose the antidepressant drug fluvoxamine for early COVID-19 treatment, we decided to conduct a clinical trial. The underlying idea was that fluvoxamine, a serotonin reuptake inhibitor, also activates the sigma-1 receptor. This receptor is involved in modulating the immune system, and a 2019 publication showed that fluvoxamine could prevent deterioration in sepsis by this mechanism (https://pubmed.ncbi.nlm.nih.gov/30728287/). We hypothesized that fluvoxamine

prescribed to COVID patients with mild symptoms early in their illness would prevent the clinical deterioration that is often seen around the second week of the illness due to an out-of-control immune response. Ultimately our clinical trial was a success: a positive preliminary finding https://pubmed.ncbi.nlm.nih.gov/33180097/ which was replicated in a larger study conducted in Brazil https://pubmed.ncbi.nlm.nih.gov/34717820/ .

We first came up with the idea for the study in late March 2020, and by early April, we had created a study protocol and gotten it approved. The protocol called for a rigorous test of 15 days' treatment of fluvoxamine for individuals who recently became symptomatic with COVID-19 but were not yet seriously ill. We would test fluvoxamine against a placebo comparator, providing more high-quality evidence than can be obtained from observational studies. We actually recruited our first participant only 16 days after our first conversation about using fluvoxamine for COVID-19. This rapid onboarding was due to the efficiency of our university's COVID-19 committee, which set up a system for rapidly reviewing clinical studies, and our Institutional Review Board (IRB), which accelerated their review process.

But then came the main challenge: recruitment. This has always been the bane of clinical trials. We had the staffing to randomize six patients per day and manage them in the trial, and we thought that recruitment would be rapid, estimating it would take approximately 3 weeks to randomize 152 patients. In the end, it took more than 4 months.

Our recruitment challenges were a two-fold problem: regulation and apathy. Regarding regulation, our IRB governs only one hospital in our hospital system (which is only one system

among many in the region). Thus, it proved impossible to recruit within the wider ecosystem of the numerous hospitals and COVID testing sites in the region, as we had no way to contact SARS-CoV-2 positive patients unless they were part of our university's medical school or its affiliated hospital.

We were also unable to get help from area organizations, who could have told patients about COVID-19 clinical trials but refused to do so. We were surprised by this, because we thought there would be a community "esprit de corps," and everyone would be interested in finding treatments that would diminish its adverse effects would help everyone. Moreover, we were not asking for organizations to make much of an effort, such as recruiting and consenting (this time-consuming and difficult task must be done by highly-trained research staff). Surprisingly to us, they were unwilling to participate even in terms of allowing us to post advertisements or to include a study flyer in their paperwork given to patients.

In some cases, my research team and I encountered hostility towards clinical trials. For example, when we approached the County health department, they stated they would not help and that it would be unethical for them to even tell patients about the existence of COVID clinical trials. They stated they would only tell patients about clinical trials if the patient brought it up first, even while acknowledging that this never happened. This decision on their part did not appear to be due to any departmental policy. They felt this was the most ethical position, but I wondered if their paternalism was ethical; after all, by not informing a patient of the opportunity to participate in a clinical trial for their condition, they were removing autonomy from that patient. Another example was at COVID-19 testing sites; in one encounter, they told us to keep lawn signs advertising for the study away from their site.

More often the problem was apathy; “not my job” was the default. This was not universal, and a few providers not only expressed enthusiasm for the research but actually helped by referring patients. But it was far too few, compared to the providers who failed to inform their patients about the availability of clinical trials or even discouraged them from participating.

These two problems—fragmentation and apathy—are exemplary of the US health care system when it comes to research. Indeed, we don’t have a health care *system* in this country, but rather a complicated patchwork of independent operators. This contrasts with the RECOVERY study in the UK, a large platform trial testing repurposed drugs for serious COVID-19. There, they were able to get the entire country's hospitals to work together on this large RCT, randomizing hundreds of patients daily. The Chief Medical Officers of England, Wales, Scotland and Northern Ireland, and the Medical Director of the National Health Service, wrote to all doctors and, encouraged participation in COVID-19 trials. Unsurprisingly, then, most of the early findings about COVID-19 treatment came out of the UK: the effectiveness of dexamethasone, and the lack of effectiveness both for hydroxychloroquine and for lopinavir-ritonavir, for reducing morbidity and mortality in patients with serious COVID-19 (>https://www.recoverytrial.net/<).

Based on our experience, I have the following recommendations. Many of these would cost the US government no money and would save both money and lives by making clinical trials in general more efficient:

1. There needs to be a mandate – accompanied by a strong statement of support – by the US government towards clinical trials. This happened in England, and I would recommend speaking with Sir Martin Landray (who directed the RECOVERY trial) about how they were able to accomplish this.
2. A similar mandate needs to be made to hospital systems – who are huge beneficiaries of federal dollars – to work for (not against) clinical trials. This includes allowing their EHRs to be used for screening participants. Had this alone been accomplished in 2020, COVID clinical trials would have gotten much further, much faster.
3. Much of the private sector (e.g., CVS pharmacies) is similarly a beneficiary of federal largesse, and the private sector should also be told that the government expects them to participate in, and aid, clinical trials.
4. Federal funds for clinical trials need to go to teams that have a track record for conducting clinical trials. This seems obvious, but the fact is the most clinical trials fail due to poor recruitment, retention, or rigor, and the main reason for this is lack of expertise – and experience – in clinical trials by the PI and their team.
5. Over-regulation of clinical trials remains a problem that only seems to get worse. Simpler rules that focus on real risks and valuable oversight would improve the pace and reduce the cost of trials.
6. Finally, the FDA needs a clear and simple pathway for approval for new indications of repurposed drugs, especially when already FDA-approved for other reasons. This would ensure that clinical trials of these drugs have a purpose: towards

implementation of the medications into health care if they are demonstrated efficacious.

I am happy to speak with the FDA further about my team's experience.

Thanks

Eric Lenze MD

OUTLINE

1. INTRODUCTION
2. ATTRIBUTES OF CTSA NETWORK AS AN EMERGENCY RESPONSE NETWORK
3. SHORT CASE STUDIES
4. ADVICE FROM CTSA PROGRAM FOR A NATIONAL RESPONSE APPROACH
5. TACTICS THAT MAY OR MAY NOT INCLUDE THE CTSA TRIAL INNOVATION NETWORK

Response to Office of the Whitehouse Science Advisors RFI

1. Introduction

On behalf of the CTSA Steering Committee and the Trial Innovation Network we are providing the following comments.

The CTSA Trial Innovation Network had substantial experience in leading COVID related clinical trials and also coordinated the process by which academic medical centers responded to the COVID-19 pandemic with novel, mechanistically targeted, randomized clinical trials and other trial related efforts. The Trial Innovation Network has similarly had a leadership role in support for comparative effectiveness trials funded by the NIH HEAL program to address the national opiate misuse epidemic.

The Trial Innovation Network is the CTSA's clinical trial support unit consisting of three Trial Innovation Centers, one Recruitment Innovation Center and all of the 60 CTSA Hubs based in academic medical centers. The most recent COVID pandemic highlighted a weakness in national preparedness, the need to be prepared for a novel disease state for which there is no evidence-based treatment. A deficit in this type of detailed evidence can only be addressed by multisite randomized clinical trials. Without robust RCT generated evidence, the American public will not accept and adhere to new treatment pathways. Hence the need to engage a national base of evidence generating centers.

2. Specific attributes of the CTSA network for emergency response include:

a. 60 academic health centers that reflect the geography of the United States
b. Together these centers and their affiliates take care of at least 93 million patients. Only 11 states do not have a CTSA Hub or an affiliation with a CTSA Hub.
c. The demographic characteristics of these patients nearly reflect the US population with 13% African-American, 6% Asian-Americans, 2% American Indian and 13% Hispanic. Seventeen percent of the CTSA patient pool reside in a rural area. Patients range from neonates to older adults.
d. Access to a large and expert research professional team with close to 750 research nurses employed by CTSA Centers and over 1000 research coordinators
e. Capability to locally Identify research teams across multiple diseases and provide support for them to participate in trials
f. Proficiency employing a robust Expression-of-Interest process by which the TIN can ask 60 sites if they would want to be a study site after sharing details of the protocol and collate responses over a period of days
g. Working Access and ongoing innovation with consortium directed regulatory resources (ex, SMART IRB and sIRB) and contracting resources for federally funded studies (FDP-CTSA) as well as Industry sponsored studies (ACTA).
h. Broad recruitment expertise both through remote approaches, use of research registries, use of EMR patient portals like myChart, and through experience prioritizing inpatient COVID-19 protocols to maximize recruitment success

i. Access to clinical research space – 689,569 sq ft. This research space was reconfigured to support clinical trials in patients with active COVID infection.
j. Support for promoting high quality data and biospecimen collection
k. CTSA Centers are leaders of use of a widely disseminated standard, REDCap, for trial data management.
l. Experience working successfully with health systems that must partner on most clinical trials
m. COVID required the identification of PIs with differing expertise and practice backgrounds. CTSAs are not an isolated unit but have the experience and structure to mobilize multiple kinds of research teams matching the needs of specific health problems. For example with the COVID pandemic there were not sufficient infectious disease specialists with the ability and time to take on the role as site PIs. Infectious disease specialists were taking on substantial clinical care obligations. CTSA leaders had to look to intensivists, hospitalists and other specialties to find PIs for the large number of studies being proposed. CTSA centers know how to work with the distributed leadership structure of most academic medical centers. CTSA centers brought in disease experts as appropriate for developing science based RCTs.
n. CTSA centers provide the know how to support Team Science and have a strong record of how to balance academic credit with the need for informative multicenter trials.
o. Commitment and success in achieving diversity of research workforce and recruitment
p. Leadership of the N3C platform to analyze a large EMR database within a protected data enclave. This platform has the potential to provide early and mid-stage data to further guide clinical trial protocol development through ease in understanding usual care and spotting trends in treatment.
q. Access to cutting edge bench research diagnostics, immunology, microbiology and cell biology to complement clinical research with mechanistic investigation.

3. Case Studies in CTSA trials Supporting National Pandemic Response

a. **ACTIV-1** was the major ACTIV trial to study the role of immunomodulators in hospitalized patients with COVID. Its platform trial design with shared placebos greatly improved efficiency. However, the limited understanding of pathogenesis at the beginning of epidemic hampered optimal study design, particularly in choice of endpoint. Given the rapidly changing landscape in an evolving pandemic with changing standards of care during the course of a trial, greater collaboration between regulators and clinical trialists would facilitate future trial innovation. A critical impediment to more rapid completion of the trial was the great variability across sites in terms of prioritization of trials and completing contacts; future responses need to address this site variability.

b. **ACTIV-6** The ACTIV 6 trial platform is widely heralded as a breakthrough to address important health questions in a trustworthy manner with rigorous randomized clinical trial arms, meaningful patient-centered outcomes, novel analytical approaches to ensure every participant counts and flexibility to reach patients or hotspots wherever and whenever they may occur. To date, over 5000 participants have been enrolled and

randomized from tens of thousands who have engaged in the platform. The trial used an innovative hybrid direct-to-participant platform that leveraged health care systems throughout the US including the CTSA's Clinical Trials Innovation Network and other health systems. We used a centralized system to enable engagement, consent, randomization wherever a participant lived throughout the United States. Combined this has created a "click and mortar" model that can be repurposed across different health conditions.

c. **CSSC-01 (convalescent plasma in early COVID) & CSSC-004 (convalescent plasma for those with household exposure to COVID)** were placebo controlled trials, utilizing 25 CTSA sites to recruit 1,351 subjects in outpatient trials of convalescent plasma for patients who have early COVID. It was performed in 16 months and led to revision of the FDA EUA letter of authorization # 12282021. Important operational characteristics associated with high quality trial performance were Federal OTA flexible contracts, use of an sIRB with protocol change turnaround times of days, use of temporary out of hospital COVID positive treatment sites, robust bilingual coordinator staffing, substantial participant reimbursement and a robust link between the clinical endpoints and bench mechanistic laboratory testing. The trial led to changes in the EUA and has generated 20 peer reviewed publications to date.

d. **PassITON** There were many lessons learned during the conduct of the randomized, double blind, Passive Immunity Trial for Our Nation (PassITON) testing the concept of using plasma from patients convalescent from a recent case of COVID. Early on, the investigators discovered that both the FDA and the NIH were very keen on obtaining data from a randomized trial, and, obtaining it quickly especially since convalescent plasma had already obtained Emergency Use Approval from the FDA and was already in wide clinical use. IRB and FDA approval to conduct the trial was achieved in record time. The management of the trial by the single IRB was greatly benefitted by use the iREX single IRB portal (J Clin Transl Sci. 2022; 6(1): e39, https://www.irbexchange.org/p/) and subcontracting to the clinical sites was greatly expedited through use of the Clinical Trial Standardized Agreement (https://ara4us.org/acta/) . Existing relationships were crucial for forming a network quickly (for example, the NHLBI PETAL sites were engaged) and also allowed for targeted and direct collaboration with community and minority outreach groups. These collaborations quickly facilitated education and enrollment of underserved minority populations (which also happened to be the populations overburdened by severe COVID). In 14 months, 25 sites in the US enrolled 974 patients. Early on in the trial, it became apparent that titering of the plasma was far from standardized and, after it was discovered that most of the convalescent plasma collected was found to be of insufficient titer to be used clinically, the Rosetta Stone project was initiated to accurately identify plasma with high neutralizing titers (ref). Somewhat hampering recruitment was the availability of open label convalescent plasma. In this setting many lessons were learned and dealt with on the fly so as to keep the trial moving to rapid completion. (Chest 2022 Nov;162(5):982-994 doi: 10.1016/j.chest.2022.06.029)

e. The **ABC Science Collaborative** was a community partnership between school districts (>200), school boards, school superintendents, schools (>4,000), and CTSA sites (12) from 9 states that led a series (>20) of epidemiologic studies collecting data from over 1,000,000 school children and staff. The team (https://abcsciencecollaborative.org/) first showed that return to in-person learning was safe (published, January 2021), and then showed the effectiveness (or lack thereof) of multiple different mitigation strategies including masking, testing, lunch policies, extra-curricular activities and distancing. The team's success relied on real-time return of results to school districts, trials that addressed questions asked by community stakeholders (e.g., can we safely sit 3 children to a seat on a school bus with high COVID transmission in the community?), virtual community engagement meetings held multiple times per week across the country, and trusted 3rd party analysis of data.

f. **ACTIV 4a**. (was developed by the ACTIV4a group and was prepared for the Cross ACTIV group led by Stacey Adam) Global collaborations led to ACTIV-4a which occurred with the ATTACC and REMAP-CAP platform trials combining to form the multi-platform RCT (mpRCT). This initiative occurred very early in the pandemic and allowed for harmonization, including common primary outcomes. Utilizing a "network of networks" afforded faster start-up and allowed for use of existing collaborations and communications to rapidly build the platform team. It was critical to include long-term outcomes and QOL embedded within the master protocol and consent, which ACTIV-4a did at the outset, well prior to the knowledge that COVID-19 would have chronic consequences in addition to the acute illness. Standardized case report forms (CRFs) would be an asset to future trials. The harmonized development of the CRFs from the mpRCT has facilitated not only the prospective harmonization of trials but also secondary and meta-analyses of results. In addition, mortality and other data collected could be pooled across trials and presented to different DSMBs as long as prospectively harmonized. The use of open-label studies for repurposed drugs in hospitalized patients with objective outcome measure was easier and resulted in faster start-up.

g. Early Pooling of Data to enhance insights on Efficacy and Safety - Process and Challenges. Pandemics generate many small, underpowered, and duplicative studies/trials. NCATS through the TIN tested the CTSAs network ability to increase collaboration and cooperation around data pooling, with the goal of speeding data repurposing via reliable analyses and adjudication of data. We developed a platform to pool, analyze and disseminate data. It was tested with multiple trials from two distinct sets of COVID therapeutic data. The project produced process information regarding: PI engagement and interest in participation, IRB requirements, data harmonization process, procurement of study documents, data repository, data anonymization process, data analysis code, data use agreements, authorship decision processes. This exercise provides a tool for future epidemic and pandemic readiness with turnkey, generalizable methods that are disease agnostic.

4. Advice from CTSA Program for a National Response Approach

Institutional capability to rapidly operationalize research resources and oversight leading to pragmatic randomized trial execution

Most academic health centers worked with their CTSA centers as they responded to the COVID pandemic. However, neither the Dean's offices or the NIH institutes were certain if CTSA centers had the full responsibility to coordinate COVID clinical trials. We think with more clarity around the sequence of emergency response tasks and their execution, both the NIH and the CTSA centers could work together more efficiently. It is very difficult for academic health centers to efficiently plan for support of clinical trials when the NIH Institutes and Centers are not coordinated. In an emergency situation, the development of clinical trials has to proceed quickly. However, there was little to no input from potential study sites to the study planning committee related to assessments of protocol feasibility or competitive trials. There needs to be both a process and more effort to work with the actual clinical trial sites as protocols are developed.

Through the Trial Innovation Network the CTSA centers coordinated several multicenter clinical trials and participated in many of the NIH COVID and HEAL trials as sites. Based on this experience we have the following advice regarding critical randomized trial resources needed for a national emergency response program.

- Many CTSA Centers have formal affiliate partners that include other academic centers, community health networks and outpatient centers such as Federally Qualified Health Centers. We think many of these centers want to participate in clinical trials but their interest needs to be continuously assessed and health centers serving lower income patients will need more financial support to maintain a level of preparedness. While academic centers have a continuous commitment to research, the affiliate's interest in participating in clinical trials can quickly change based on the leadership and financial status of the affiliates. Participation in any warm base protocol will require some continuous funding. Without this funding there is no sense of obligation that would lead to predictable participation in RCTs and high adherence to task completion.
- CTSA centers have access to special populations that may be high risk, neglected (such as children), pregnant women and underrepresented minorities. One never knows what special population may be bearing the brunt of a disease. For example, the CTSA centers would be ready and able to work with older adults and transplant patients where the burden from COVID-19 has been higher.
- We think relying on one single national IRB would be too high risk operationally, because a diverse set of research evaluations is often needed. Any one IRB might not have all the personnel that would be needed, could be overwhelmed with protocols or could be out of action because of illness or personnel shortages. The Trial Innovation Network has three sIRBs with extensive cohorts of relying institutions that work in a coordinated fashion for a nationwide goal(s). They can also offload work to other IRBs when necessary. We think this is the best model for responding to emergencies.

- The CTSA network works closely with the N3C platform that includes an integrated EMR database of over 10M individuals with COVID. N3C allows the ability to conduct up to date and generalizable target trial simulations using electronic health records for faster assessment of existing therapeutics during emergencies while actual trials are being mounted/recruiting. Later N3C can help with prioritizing allocation of resources for actual trials to new therapeutics. Similarly, this capability can be used to inform interim reviews of trial performance.
- Remote trial process can potentially facilitate diverse recruitment in addition to supporting participant safety during emergencies. Remote trial operations include real time outbreak data to identify hot spots, use of social media and other online recruitment methods, community buy-in and referrals, telehealth visits, remote consenting, partnerships with courier services for sample processing, and remote monitoring capabilities. Remotely conducted trials can overcome structural barriers to trial participation while maintaining rigorous scientific methods. However remote approaches will not increase diversity without a deliberate effort to reach out and support Under Represented Minorities (URM) populations in research. Due to historic issues of trust, URM populations often require some direct communication with research teams before enrolling in clinical trials. We also encourage funding for programs to increase trust in research for URM populations that are continuous and will better prepare the nation for national emergencies. The population has to be prepared to enroll in clinical trials before they are asked during the actual emergency.
- The CTSA network has substantial experience in translation of study materials, particularly Spanish. We can translate consent form and other patient-facing documents in 1-2 weeks. National COVID studies took weeks to months which delayed recruitment for Spanish speaking individuals.

5. **Tactics that may or may not include the CTSA Trial Innovation Network**

    a. ***Preparation.*** There needs to be more advanced coordination between and across all health and biomedical research oriented federal agencies as well as all NIH institutes. **A playbook of roles and responsibilities** should be in place and agreed to in advance of the next pandemic. Having roles and plans set in advance will prevent unnecessary delays in forming new structures and agreements. In this model, the only adaptations should be to accommodate the scientific nature of the public health crisis (e.g. infectious, environmental, addiction, or other).

    b. ***Orientation.*** Equipoise in clinical research and in clinical practice is a fundamental ethical and scientific principle that exists when there is uncertainty in terms of the risks and benefits of a particular therapy. When a pandemic or other novel threat arises, clinical equipoise exists for most potential therapies. The response to equipoise should be randomized trials, not widespread use of unproven therapies. **High quality multi-site randomized studies need to be prioritized with funding.** Use of unproven therapies outside of clinical trials, which do not generate reliable evidence, *should be actively discouraged* in favor of rigorous research that can inform future practice. When uncertainty over the effects of an intervention exist, infrastructure should be in place to rigorously evaluate the intervention, in a randomized trial WITHIN clinical practice to

generate real world evidence. Patients will be receiving "treatment" for their condition, but within a clinical trial embedded within clinical practice. This is one more example where there has to more interaction with health systems as they are stressed during pandemics yet will need to have a role in how clinical trials are implemented if they are to be meaningfully engaged.

c. ***Prioritization of clinical trials by federal government.*** Global experts with experience conducting high-quality, rigorous clinical trials, rather than a governmental organization, should lead the nationally coordinated research effort. The decision-making body should have **balanced, pre-designated membership** from industry, government, academia, nonacademic health systems, and non-profit, voluntary health organizations and patient groups. Overrepresentation of industry may incentivize research on proprietary and early stage investigational medicines to the exclusion of available medicines and devices. Notably, the majority of agents ultimately shown to improve inpatient outcomes in COVID-19 (corticosteroids, COVID-19 convalescent plasma, anticoagulation, tocilizumab) were available prior to the pandemic. Outpatient randomized clinical trials to prevent progression to hospitalization should have more priority early during the emergency rather than the passive implementation of patient presentation to hospitals. The public benefits more with outpatient preventions like vaccines or outpatient early therapy.
d. ***Federal regulations.*** FDA and OHRP **regulations need more flexibility** in the context of the pandemic. Otherwise, they can present a barrier to the type of "point-of-care" pragmatic trials that can readily inform care rapidly. Excessive regulations may limit opportunities to streamline clinical trial contracting, data capture (Part 11 compliance) as well as the ability to rapidly support novel informed consent approaches (e.g., EFIC, alteration, waiver). Federal regulatory requirements on what is needed in consent forms and limitations on who could perform consent (i.e. key study personnel) limited the flexibility needed to efficiently and rigorously conduct pragmatic trials in the United States. Regulation need to be flexible on remote e-consenting especially using a cell phone. The ICF should be limited to 2-3 screens with big font maximum, and the most important information has to be fitted into these screens. Many URM patients are very distrustful when the ICF has many pages and many boxes to chat . They just give up." Flexibility in consenting was critical to the success of efficient point-of-care pragmatic trials conducted by other countries (e.g., the RECOVERY trial in the UK).

e. ***Therapeutic and management strategy prioritization.*** We propose that an unbiased and independent group (e.g., not associated with any of the agents being proposed) prepare summaries and **facilitate a standardized and consistent therapeutic review process**. This allows open access to any recommended potential therapy and does not rely on each therapy to have an incentivized champion. These reviews should be ongoing in pilot efforts, early review of multisite RCT effort and mid effort review. These reviews should be informed by both the trial data and population-based data as was acquired by NC3 or other designated resources with ongoing active programs and the ability to provide up to date credible data on a weekly basis. Similarly, including research on supportive therapies and/or comparative effectiveness of existing management strategies should be enabled by a standardized process (i.e. we should not only focus on new drug and device development). A diverse panel of antibody based (vaccine, monoclonals or convalescent plasma) or biologically plausible drug therapies

which are rapidly deployable as a first steps needs to be prioritized for pre-pandemic readiness.

f. ***Awareness of resources.*** It was clear that among the organizations able to participate in research in the U.S., there are so many disease-specific research networks that it was challenging to identify sites for participation in new studies using existing networks, which overlapped and were configured around a specific pre-pandemic patient population. All elements of any national consortium need an up-to-date, **single database view of all active research networks**, focus areas, enrollment rates, and expertise. The ACTIVE trials pivoted from HIV research. Present large disease specific trial networks should develop dual capability to be able to pivot to a pandemic.

g. ***Community engagement.*** One of the most important lessons in the pandemic was the lack of engaged community populations which took a negative toll on all research. Once recognized, attempts to affect change in this space was sometimes seen as 'too little, too late' or led by individuals with no experience in this area. Community engagement must be approached with cultural humility, with the **commitment to build and sustain trust over time**, effective bi-directional communication, and co-learning for mutual benefit. These cannot be jumpstarted and must be longstanding collaborations. Principles of community engagement which maintain that stakeholders are valued, respected, and compensated for their contributions to research and not engaged after the fact. Engaging diverse stakeholders requires time, expertise, and resources and acknowledges that African Americans, Hispanics, other ethnic groups, rural and other communities often bear a greater burden of disease.

h. ***Readiness to activate.*** We agree with the concept of "warm base" research which could build enrollment capacity, improve clinical practice between pandemics, compete for independent funding for large pragmatic trials, and form **the foundation of future research cooperatives for the next pandemic.** Such warm bases would be sustained sources of institutional expertise in all critical aspects of trial conduct including: regulatory experience, flexible and facile investigational drug pharmaceutical services, capabilities for rapid implementation in clinical information systems (such as for randomization schema and order sets), statistical design expertise, automated data capture tools, regulatory-acceptable eConsent tools, skilled coordination staff, efficient contracts management, patient engagement, dexterity in dissemination of findings, single IRB structure and associated reliance agreements, as well as existing and contemporary contractual agreements. A component of the warm base should be exercises in pivoting to pandemic trials. The infrequent pandemic exercises with military, government and academic centers also need to focus on implementation of outpatient randomized clinical trials.

i. ***Expertise identification.*** Because the nature of the next pandemic is unknown, a **mechanism to identify experts across any content area** is needed both for steering committees and local investigators. The Trial Innovation Network (TIN) is ideally suited to identify and leverage researchers across their local sites. As a disease agnostic infrastructure, it has mechanisms to find mechanistic expertise within each major academic medical center. An ongoing expert and site selection process is continuous and is instrumental in identifying interested and engaged sites. This systematic process has been utilized in ~59 TIN supported studies in the past 6 years. This process was

utilized during the pandemic in 11 trial instances, but predominately too late in the course of pandemic organizational events to produce a strong feasibility influence.

j. ***Organizing master protocols/platforms.*** We agree with the concept of drafting **master protocols that can accommodate multiple therapies** for the same novel disease with definitive clear endpoints like hospitalization or death rather than symptom resolution or microbial clearance. When deployed in the context of a platform, these master protocols can offer efficiencies in both trial operations and scientific efficiency with regard to information learned per enrollment. A Master Protocol can also support the use of common outcomes to facilitate making comparisons across interventions. In a single platform where interventions for the next pandemic could be tested in parallel or sequentially. Completion would be faster and more assured. The TIN has experience with 3 studies using master protocols for COVID and has been able to effectively disseminate timely results to facilitate change of health care practice for several therapeutics.

k. ***Study design.*** Clinical trial protocols are one of the most important elements of study conduct and take time to develop in a way that balances pragmatism with information capture - we propose a funding mechanism to launch **expert protocol drafting sprints** that would occur in parallel with network development and site selection. Endpoint definitions are important for early definitive efficacy determination. The TIN's Trial Innovation Centers and Recruitment Innovation Center have received almost 400 study submissions and have provided consultations addressing individual study design challenges and optimization in over 155 studies since its inception in 2016. We also did about 15-20 COVID trial consults, but the knowledge and use of this process was underutilized.

l. ***Leveraging low touch approaches***. Protocol designers would benefit from **consensus criteria in terms of what interventions can leverage lower touch designs** to reach remote populations. The ability to assess interventions for placement in a low touch approach (e.g., safe generic medications, low need for clinical monitoring, and shippable, self-administered agents) as well as study purpose and analysis plan (can accommodate uncertainty in adherence and other medications taken) will be vital. In these models, study evaluations are completed remotely, and medications are shipped to participants, and automated data collection methods are deployed.

m. ***Local human subjects review processes.*** While single IRBs (SIRBs) have the opportunity to streamline the human subjects review process and reduce duplication, local Human subjects Research Protections Programs (HRPPs) review is often required at each Institution which can cause substantial delays. Implementing a **system that captures each local Institutional Review Board ancillary committee reviews** with transparency in the review process will be instrumental in providing clarity in obtaining those local reviews in parallel with SIRB activities. A system where study sites can learn from each other in the local context review would help develop new standards for local context review. In addition, identifying a suite of experienced SIRBs, both academic and commercial, available to manage these activities is imperative.

n. ***Data collection infrastructure.*** Efficient, high-quality, real-time data are critical for rapid trial planning, trial monitoring, and trial adaptations. We need better investment to create the **automated electronic data extraction tools necessary for generating**

answers in real time by implementing a system to achieve real-time automated extraction of data from the EHR. N3C provided a federated solution and REDCap is another widely used and freely available data collection platform providing a more distributed solution. Coupling data collection with more coordination of common outcomes and standardized assessment tools will increase the utility of each clinical trial. In addition, it will be important to emphasize collecting race, ethnicity, preferred language, and social determinants as well as having the ability to stratify and disaggregate by these elements.

o. ***Generalizability of findings.*** Research intensive institutions need funds to **bring in diverse sites** to be part of the process for prioritization and feasibility. CTSAs have affiliate sites that can increase reach to diverse, underserved, vulnerable populations and most have existing relationships with community groups that can be leveraged during these events. The conduct of point-of-care pragmatic trials through "warm sites" would also benefit from preexisting cooperation from health systems. Coupled with funding these relationships, there is a national need for flexibility on structure/process that enables enrolling sites among organizations not traditionally conducting research, such as better delineation of regulatory applicability based on granularity of roles. There will need to be mechanisms to transfer funds directly to community organizations and not have to funnel through academic institutions. Nonacademic organizations will usually not start work until funding has been received. Additional **funding for dedicated recruitment support** including for marginalized, non-English speaking, and underrepresented populations that might be at greatest risk, will be critical for generalizability. The TINs Recruitment Innovation Center (RIC) has developed many recruitment-related data tools and resources available for public consumption (FasterTogether, ResearchMatch, REDCap TrialsToday, FHIR clinical data-based recruitment infrastructure). These innovations acknowledge recruitment is not a one-time activity but is a continuous process that needs to adapt as the study is conducted.

p. ***Activation processes for networks and sites.*** Mechanisms for rapid funding from the federal government and other sources are critical as most research institutions have no compliant way of starting the necessary work without a notice of funding from federal agencies. An **Emergency Master Agreement** is essential; this type of agreement currently exists for federally funded studies (FDP-CTSA) as well as Industry sponsored studies (ACTA). These agreements contain all the terms needed for a clinical trial agreement and have already been accepted for use by over 350 organizations/ institutions in the US. The TIN was able to use the FDP-CTSA agreement in several COVID studies which offered a tremendous time savings. In addition, the TIN has created an "Accelerated Start Up" process and has demonstrated a 90 day start up for individual sites.

q. ***Special and vulnerable populations historically neglected in clinical research.*** Special populations (e.g., children, pregnant women, prisoners, chronically ill and disabled) require dedicated support and expertise in order to ensure high quality research that improves public health for these individuals. These populations have special challenges that need to be addressed in the emergency trial capacity setting, including: unique physiology and response to therapeutics, ethics of informed consent, limited existing infrastructure, limited number of potential research participants, and a limited number

of qualified investigators. In several such populations the TIN was able leverage its expertise and infrastructure to support multiple federally sponsored studies (including COVID), and to help support the ABC Science Collaborative define an evidence-based, community acceptable, path to school opening in the COVID pandemic

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December 28, 2022

Response For:

Request for Information; Clinical Research Infrastructure and Emergency Clinical Trials
Office of Science and Technology Policy

Submitted By:

Institute for Advanced Clinical Trials for Children (I-ACT for Children)
9200 Corporate Blvd
Suite 350
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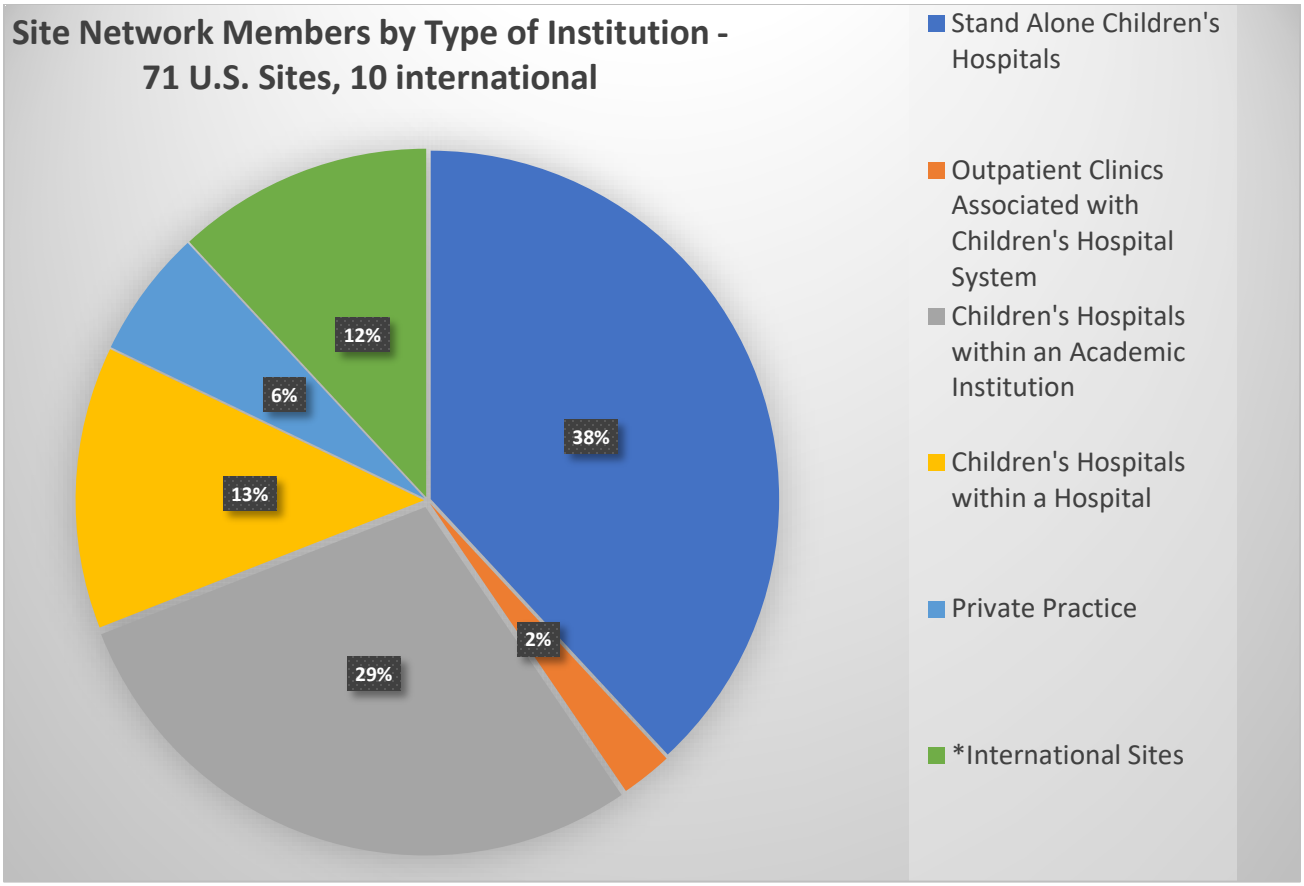
To Whom it May Concern:

The Institute for Advanced Clinical Trials for Children was formed and incorporated as a 501(c)3 nonprofit organization with a mission to serve the pediatric community as an independent and connected organization to accelerate the clinical development of innovative therapeutic solutions to improve health outcomes in children. I-ACT for Children was originally formed with funding from a 5-year Grant from the United States Food and Drug Administration (Grant #5U18FD006297). This grant called for the formation of a clinical trial network that could perform clinical trials that would fulfil regulatory requirements for drug approval.

A pediatric clinical trial site network infrastructure was formed which currently includes 71 US-based pediatric clinical trial sites and 10 international sites based in Australia, Latin America, South Africa, and Saudi Arabia. I-ACT for Children also has collaboration agreements in place with pediatric clinical site networks in Canada, the Maternal Infant Child and Youth Research Network (MICYRN) and the Belgium Pediatric Clinical Research Network (BPCRN) in Europe currently serving as the coordinating center for the European clinical trials sites in the Connect 4 Children (c4c) Network. Most of the institutions are children's hospitals or related institutions and university-based children's hospitals. A breakdown of our current site network is noted below.



A listing of our clinical trial sites can be found on our website at: https://www.iactc.org/our-capabilities/global-pediatric-research-site-network/. The sites are well placed to allow participation of diverse populations as they are generally the major pediatric institutions in their regions. In addition, I-ACT for Children has formed a Diversity Panel to assist with issues that impact diversity in clinical research. Further information on the Diversity Panel can be found here: https://www.iactc.org/about-us/advisory-committee-and-external-advisory-panels/

Our initial site interactions are coordinated by a Site Point of Contact (POC). The POC is generally a lead study coordinator or operational head of the clinical research trial office of that institution. In addition, we have an assigned Site Champion (SC) who is either a physician or PhD who leads the institutional clinical research efforts for their specific institution and can be called on to mitigate any overarching issues noted. They also serve as a representative of I-ACT for Children within their organization. The POC routes the information survey to appropriate divisions or individual Principal Investigators for review and completion. The surveys are completed quickly, and information obtained in a timely manner to facilitate rapid site

identification. Our internal Site Network Team coordinates and collates this information for communication to appropriate individuals or organizations.

All the sites have had extensive site initiation visits with most of them on-site to assure they are capable of performing regulatory grade research as well as assure they have the personnel, procedures and equipment available to perform a pediatric clinical trial. The majority of our sites are enrolled in the Shared Investigator Platform Program (https://www.transceleratebiopharmainc.com/initiatives/shared-investigator-platform/) and also capable of using a Central IRB.

Our pediatric clinical trial site network is provided the opportunity to participate in educational events, trainings, an extensive mentoring program as well as a quality improvement program. The quality improvement program design reflects both the Institute of Medicine's (IoM) Learning Health System and the Institute of Healthcare Improvement's (IHI) Breakthrough Series Collaborative methodology.

We have established a robust system for communicating with the sites including the ability to rapidly deploy and collect survey information from the sites. These surveys include interest in upcoming projects, feedback on events and information about clinical trial feasibility for specific projects. We feel our communication platform, the internal POCs and SC who facilitate this contact would fulfil the requirement of any emergency need and could rapidly respond to queries of interest.

In several instances, we have successfully collaborated with our international site network partners BPCRN and MYCRN to identify pediatric clinical trial sites for a variety of therapeutic areas including COVID therapies. These projects have been coordinated and managed by internal I-ACT for Children staff. We believe we are already facilitating foreign participation in clinical trials that originate in the US and could build upon this expertise with the formation of an Emergency Clinical Trials Research Network.

The I-ACT for Children Site Network is perfectly placed to become an integral part of an overall Emergency Clinical Research Network Infrastructure for the following reasons:

1. The site network was conceived and formed to facilitate the conduct of registrational clinical trials for children
2. The pediatric clinical site network is already in use and performing regulatory grade pediatric clinical trials in a variety of therapeutic areas
3. The sites are pre-qualified, experienced, and educated in the conduct of pediatric clinical research
4. The sites can use a Central IRB if necessary
5. Availability of a Diversity Panel to consult and advise on diversity related issues and concerns

6. Current experience with working internationally with other pediatric research networks.

In conclusion, we feel that I-ACT for Children's Site Network can play an important role in an Emergency Clinical Research Network and form the backbone of the pediatric portion of the network. We look forward to further collaborations on this interesting and necessary project.
Respectfully submitted,

Cindy Jackson, D.O., F.A.A.P
Chief Operation Officer

Alex Lebeaut, M.D.
Chief Executive Officer

Of the past 6 who global health emergencies, 3 (H1N1, Zika, and COVID) have had more severe or unique impacts on pregnant women. Yet pregnant people and people who could become pregnant were systematically excluded from clinical trials.

We had to triangulate that Pfizer was safe from vaers, observational mechanistic sisters (like ours on placenta) and cohort studies that reported sorry millions of patients were exposed.

It is clear that the alternative to exposing these patients to the risk of a randomized clinical trial is not to avoid exposure, but to expose a larger group to an unrandomized, uncontrolled observation.

I think we can do better:
. End routine exclusion of pregnant and nursing patients from clinical trials
. Fund or mandate inclusion of pregnant and nursing patients in clinical trials
. Lay out adequate materials to check as early biomarkers of adverse outcomes (maternal and cord blood, placenta, milk)
. Consider mechanisms to limit liability for well designed, emergent studies in pregnant and nursing patients.

Thank you,
Jeff

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Dear Dr. Sipes,

Thank you for the opportunity to respond to the RFI on Clinical Research Infrastructure and Emergency Clinical Trials. We appreciate OSTP's leadership on this issue and in recognizing the urgency to implement solutions that address major gaps in the pandemic response.

Several of our proposed solutions for clinical trial reform were outlined in a piece that was published in *Nature Medicine* "A US Clinical trial network is needed for the next pandemic" (Vol 28, Jul 2022, 1329-1334). Our recommendations were based on i) challenges that we and many others directly encountered to bring COVID-19 therapeutics into clinical trials; ii) observations and results that were successfully achieved in other countries, namely the UK Recovery Trial; and iii) discussions we have had with colleagues in the federal government, academia, and the private sector about feasibility and infrastructure that exists here in the United States.

As stakeholders from an academic research institution, we appreciate your time and interest to hear our perspective. In the response, we highlight some of our recommendations from the *Nat Med* piece, but also discuss specific opportunities to expand the US clinical trial capacity by tapping into more than 6,000 acute-care hospitals in the country that were largely left out of participating in COVID-19 clinical trials.

Feel free to contact me with any questions or comments – I look forward to continuing the discussion with you as this important initiative moves forward.

Best wishes,

Kevin V. Grimes

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Response to OSTP Request for Information on Clinical Research Infrastructure and Emergency Clinical Trials

Governance for emergency clinical trials response.

As described in detail in the RFI, a new approach is needed to coordinate clinical trial research to identify safe and effective therapeutics to contain a pandemic. We believe that the focus should be on a nation-wide network of clinical sites trained to conduct adaptive multi-arm platform trials designed for simplicity of enrolment and data collection (1). Our recommendations are guided by the following design principles: i) an emphasis on expanding the network that reaches all parts of the country, specifically regions that have traditionally not participated in clinical trials and ii) implementation of policies and practices that focus on the most meaningful patient outcomes. These priorities reflect the need to seamlessly integrate clinical trials into the workflow of a healthcare system that would be under stress.

To quickly identify and evaluate treatments that are effective in diverse populations like the US, a real-world study with hard clinical endpoints would be the most effective (1, further discussed below). As the UK Recovery trial demonstrated, it is possible to obtain actionable information on effective treatments quickly if the clinical trial is carefully designed to minimize additional workload on an already stressed healthcare system. The UK trial was able to evaluate six treatments in a head-to-head comparison with standard of care as the control arm in record time. RECOVERY enrolled 7,586 patients across 172 sites within 1 month of ethics committee approval of the protocol (2) and within 3 months, the study had generated sufficient data to draw two important conclusions: dexamethasone was effective in reducing mortality, whereas hydroxychloroquine was not (3, 4).

In the United States, the lack of an existing, centralized clinical trial infrastructure put us at a disadvantage, and we were far behind the UK in clinical testing of therapeutics. In the US, there exist more than 6,000 acute-care hospitals, and over half have more than 100 beds. Most of these hospitals did not enroll patients in COVID-19 trials. The US clinical trial infrastructure should be increased by *expanding* the capabilities of these acute-care hospitals. All acute-care hospitals with over 100 beds and accountable healthcare organizations that receive Centers for Medicare and Medicaid Services (CMS) funding should be required to have a clinical trials office (CTO) prepared to conduct inpatient and outpatient studies, with funding and training for staff provided by the federal government. Training for the CTO staff can be provided through web-based materials and virtual educational conferences. This will provide added benefit to the national clinical research enterprise by providing a "warm base" to support real-world studies of new therapies and comparative effectiveness studies.

This effort could be established under the oversight of the White House Office of Pandemic Preparedness and Response Policy that is proposed in next year's federal funding package and will require input and cooperation from multiple existing federal agencies including: NSC and its Directorate for Global Health Security and Biodefense, DPC, FEMA, HHS, NIH,

CDC, FDA, CMS, and PCORI. CMS could share data that pinpoints hospitals and health care systems that meet the criteria for inclusion in the expanded network. PCORI could provide guidance regarding coordination of a national network and ensuring that diverse patient populations are included. NIH can share information and experience from its directory of existing sites from large clinical trial networks that it supports. Expanding and coordinating this pandemic network will not be achievable overnight, or even when an outbreak emerges, and would need to begin now.

Clinical Trial Design

Starting with the Patients and Providers in Mind. During the early months of the COVID-19 pandemic, the UK RECOVERY investigators designed a master protocol that revolved around the workflow of patient care. To facilitate participation, the master protocol was designed to enable providers to focus on treating patients, with few deviations from standard practice — any additional work for participating in the trial was limited to data entry and training of staff that could be accomplished in minutes, use of simplified patient consent forms and randomized assignment of treatment (2), in order to maximize enrollment. Although blinded clinical trials are considered the gold standard, under pandemic circumstances an open-label trial was readily integrated into standard care, allowing providers and patients to understand the risks and benefits of the treatment, and providing a level of transparency that facilitated participation in the trial. The large enrollment numbers and hard clinical endpoints, such as mortality, days in the ICU, *etc.,* in UK RECOVERY compensated for the potential confounders of an open-label trial. A similar approach, focused on simplicity of enrollment and data collection from the patients' and practitioners' perspective should be prioritized in clinical design choices during a pandemic.

This would include the use of off-the-shelf adaptable and simplified multi-arm master protocols and with multiple master protocols running in parallel. A centralized Institutional Review Board (IRB) and contracting process will facilitate study start-up. Under the expanded clinical trial network, all CMS-supported healthcare facilities should prioritize enrollment of patients into master protocols. This will help to reduce multiple clinical trials competing for the same patients and resources, and to avoid underpowered clinical trials.

Document templates, including protocol, investigator brochure, informed consent and case report forms, can be prepared in advance and then tailored to each specific study. A minimal dataset regarding patient outcomes should
be entered into a centralized study data-management system to answer safety and efficacy questions as expeditiously
as possible. Such real-world master protocol studies will lower costs, reduce duplicative efforts, increase the rate of patient enrollment, improve quality of evidence and provide results in a compressed timeframe.

Agent selection criteria

Encouraging transparency in the process. In our discussions with other research centers and with small and medium sized biopharma companies, there was a keen interest to participate in platform trials and clinical trial networks like NIH ACTIV, but this was countered by the general sense that there was a lack of transparency on how therapeutic agents were being evaluated, who was doing the vetting, whether there were conflicts of interests, and lack of clarity on how to engage the system. Study drugs should be assigned to the master protocol by an expert panel based on scientific merit, expected clinical impact, and the ability to scale-up manufacturing of the drug quickly. The selection process should be transparent with pre-determined criteria for acceptable safety and efficacy. The ability of industry to pay for the clinical trial should not be a major factor for agent selection. The expert panel should reflect a broad set of expertise including infectious disease, intensivists/ICU physicians, product development, regulatory, clinical trialists, public health/epidemiology, and patient perspectives such as a representative from centralized IRB.

Repurposed drugs with ample safety data could be seamlessly integrated into simplified master protocols. New experimental agents including monoclonal antibodies and anti-viral agents that require more extensive data collection regarding patient safety and optimal dose selection can be entered into adaptive trials where first-in-human studies are conducted at a subset of experienced clinical sites followed by expansion into the larger network once safety and optimal dosing have been established.

Activating the Trial Network System

Perhaps the most politically acceptable time to activate the national trial network would be when clinical sites in any US region are at risk of being overwhelmed by pandemic patients. A more proactive approach, however, might lead to earlier identification of effective treatments and save lives. In this scenario, the network should be activated and placed on standby once health care systems outside of the US are being overwhelmed in a pandemic. The platform trial would be activated at individual sites as soon as pandemic patients begin to present. This would allow clinical sites to become adept at implementing the multi-arm protocol before facing an onslaught of patients. Sharing this approach and related materials with international colleagues to develop a shared global platform might save additional lives and resources through even earlier identification of effective therapies.

In summary, a new clinical trial paradigm is required for the next pandemic that includes a nation-wide network of clinical sites with a common goal of expeditiously conducting adaptive multi-arm platform trials designed for simplicity of enrolment and data collection that will sequentially evaluate the most promising therapeutic candidates.

References:
1. Yajima R. et al. *Nat Med* 28; 1329-1334 (2022)
2. Wise, J. et al. *BMJ* 370, m2800 (2020)
3 Wilkinson E. *BMJ* 369, m1626 (2020)
4. RECOVERY Collaborative Group. *N. Engl. J. Med*. 384, 693–704 (2021)

To: emergencyclinicaltrials@ostp.eop.gov

Re: Emergency Clinical Trials RFI

We write to highlight the need for an ethical framework to guide when to include pediatric populations in clinical trials. Such a framework is needed to facilitate coordinated, large-scale clinical research to address an outbreak of infectious disease or public health emergency. This comment relates to the following topic: (1) Governance for emergency clinical trials response, (h) Best practices for designing trials that can enroll vulnerable populations, such as the pediatric population, as needed in particular circumstances.

Existing ethical frameworks generally recommend conducting research in adults first, and then progressively enrolling children at younger ages (i.e., "age de-escalation"). The resulting practice of systematically delaying pediatric research fails to adequately address the impact of infectious disease outbreaks, public health emergencies, and disasters on children.

For example, in the COVID-19 pandemic, Operation Warp Speed had initially planned to complete adult testing before enrolling children in vaccine research. This decision was based on early estimates of the risk of severe disease in children. However, that approach failed to consider the indirect effects of public health measures on them and the unprecedented nature of considering public health reasons to enroll children in vaccine trials sooner. The decision to take a precautionary approach to pediatric research on COVID-19 was not revisited until the Fall of 2020, which delayed access to vaccines for children. (*See* Mintz K, Jardas E, Shah SK, et al. Enrolling Minors in COVID-19 Vaccine Trials. Pediatrics. 2021;147(3):e2020040717). Furthermore, while some trials enrolled participants down to the age of 16 from the start, others waited to enroll adolescents, without any clear reason for these differences.

A comprehensive, stakeholder-engaged framework to guide ethical pediatric involvement is sorely needed. This framework should distinguish between treatment and prevention. It should also offer nuanced recommendations based on the type of disease or intervention and different developmental stages. The age of 18 is not a bright line, and adolescents younger than 18 may have decision-making capacity similar to adults. The biological similarities and differences between adolescents and adults also need to be taken into account as they relate to the pathophysiology of the disease in question. (*See* Nachman S, et al. Towards early inclusion of children in tuberculosis drugs trials: a consensus statement. Lancet Infect Dis. 2015;15(6):711-20.)

The indirect effects of public health interventions like school closures on children should also be weighed in decisions about when to engage children in research, along with the public health justification of giving vaccines to children to protect others and limit disease transmission at the population level.

The only existing framework for when to initiate pediatric research is focused on treatment, rather than vaccines, and was published more than fifteen years ago without a process to engage stakeholders. (*See* Gill D. Ethical principles and operational guidelines for good clinical practice in paediatric research. Recommendations of the Ethics Working Group of the Confederation of European Specialists in Paediatrics (CESP). European journal of pediatrics. 2004; 163(2):53–57.)

In sum, there is urgent need for a framework to guide the initiation of pediatric research that is responsive to contextual factors arising in different emergencies and informed by mistakes made in the COVID pandemic. A new framework for pediatric research should therefore: (1) engage stakeholders, (2) not treat the age of 18 as a bright line for exclusion, (3) consider broader public health needs, and (4) account for the direct and indirect effects of public health interventions.

Seema K. Shah, Ravi Jhaveri, Larry Kociolek, and Jennifer Kusma, of the Pediatric Research Ethics and Policy (PREP) Program at Lurie Children's Hospital of Chicago

Mitchell Berger
Rockville, MD
November 27, 2022

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Request for information (RFI) on clinical research infrastructure and emergency clinical trials (87 FR 71368), https://www.federalregister.gov/documents/2022/11/22/2022-25163/request-for-information-clinical-research-infrastructure-and-emergency-clinical-trials

Dear Ms. Sipes: In response to the OSTP's above RFI I write to: A. suggest that the "potential governance models for the emergency clinical trials effort" and warm base research include clinical studies and research on neglected tropical diseases; B. Consider including behavioral health research among 'warm base' clinical research activities and consider Community Mental Health Centers (CMHCs), Substance Use Treatment Centers, Certified Community Behavioral Health Clinics (CCBHCs) and Opioid Treatment Centers as potential study sites along with such networks as federally qualified health centers; and C. Support drug, biologic and medical device repurposing studies.

A. **Support 'warm base' research on neglected tropical diseases (NTDs)**: As explained in the RFI, warm base research is "a term used to refer to studies that not only gather data under a particular clinical research protocol, but also serve the function of keeping trial sites in a state of readiness to undertake additional or future research. 'Warm base' studies could address infectious diseases such as influenza, or other medical conditions that are of interest to researchers and communities, such as cancer and heart disease." The RFI also seeks comments under the heading of warm base research on "Disease areas that are most relevant to communities, including underserved communities and those that may have little experience with participating in clinical research."

Both FDA and the World Health Organization (WHO) have developed lists of NTDs. FDA includes such diseases as Filoviruses (e.g., Ebola), Zika, Brucellosis, Tuberculosis and Malaria. Developing treatments for such conditions may qualify a sponsor for a tropical priority review voucher.[1] WHO has identified 20 top NTDs with global impact.[2] The WHO list includes some of the same conditions as FDA but the two lists are not identical. For instance, WHO includes snakebite envenoming while FDA does not. WHO also has developed a roadmap calling for new diagnostics, intranational and international coordination, therapeutics and surveillance to help mitigate NTDs.[3] Brucellosis, included on the FDA list, recently infected as many as 10000 persons in China, possibly attributable to a lab-involved disease outbreak.[4] Tuberculosis is a leading cause of morbidity and mortality worldwide and significantly impacts vulnerable populations in the United States such as those with HIV/AIDS, homeless, persons with

[1] https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/tropical-disease-priority-review-voucher-program
[2]https://www.who.int/health-topics/neglected-tropical-diseases#tab=tab_1
[3] Ending the neglect to attain the Sustainable Development Goals: A road map for neglected tropical diseases 2021–2030, WHO, https://www.who.int/publications/i/item/9789240010352
[4] Georgios Pappas, The Lanzhou *Brucella* Leak: The Largest Laboratory Accident in the History of Infectious Diseases?, Clinical Infectious Diseases, Volume 75, Issue 10, 15 November 2022, Pages 1845–1847, https://doi.org/10.1093/cid/ciac463; Zhao C, Liu K, Jiang C, Wei X, Song S, Wu X, Wen X, Fu T, Shen L, Shao Z, Li Q. Epidemic characteristics and transmission risk prediction of brucellosis in Xi'an city, Northwest China. Front Public Health. 2022 Jul 22;10:926812

substance use disorder and incarcerated populations.[5] Malaria is a leading cause of death worldwide, especially in parts of Africa and heavily impacts pediatric populations.[6]

According to one review up to 1/6 of the world's population is afflicted by an NTD.[7] NTDs, including those which are vector-borne, such as Dengue, Zika, Chagas, and chikungunya are "diseases of poverty" both in and outside the United States and thus disproportionately impact lower income and underserved communities.[8] With climate change impacts and travel and migration, the range and infectivity of many diseases such as malaria and many other pathogens may increase.[9]

Zika Virus is one example of a disease (considered an NTD by FDA but not on WHO's list) that was problematic outside the US such as parts of the Western Pacific and South America before impacting the United States, especially Puerto Rico.[10] Ebola virus disease outbreaks also have caused worldwide and a WHO declarations of public health emergencies of international concern.[11] Both diseases are on FDA's tropical disease priority voucher but not specifically recognized by WHO as NTDs.

Focusing 'warm base' clinical research on NTDs can perhaps help avert new epidemics and pandemics while also developing new treatments for worldwide causes of morbidity and mortality, strengthening public health and US global diplomacy efforts.[12] As well, this effort could be an opportunity for FDA to consider updating its July 2014 guidance, Neglected Tropical Diseases of the Developing World: Developing Drugs for Treatment or Prevention, which is primarily geared toward sponsors and stakeholders operating outside the United States.[13]

[5] https://www.who.int/news-room/fact-sheets/detail/tuberculosis; https://www.cdc.gov/tb/statistics/reports/2020/Exec_Commentary.html

[6] Mace KE, Lucchi NW, Tan KR. Malaria Surveillance — United States, 2018. MMWR Surveill Summ 2022;71(No. SS-8):1–29. DOI: http://dx.doi.org/10.15585/mmwr.ss7108a1; https://www.who.int/news-room/fact-sheets/detail/malaria

[7] Mitra AK, Mawson AR. Neglected Tropical Diseases: Epidemiology and Global Burden. Trop Med Infect Dis. 2017 Aug 5;2(3):36

[8] Hotez PJ, Jackson Lee S (2017) US Gulf Coast states: The rise of neglected tropical diseases in "flyover nation". PLoS Negl Trop Dis 11(11): e0005744. https://doi.org/10.1371/journal.pntd.0005744; Hotez PJ (2008) Neglected Infections of Poverty in the United States of America. PLoS Negl Trop Dis 2(6): e256. https://doi.org/10.1371/journal.pntd.0000256. Athni TS, Shocket MS, Couper LI, Nova N, Caldwell IR, Caldwell JM, Childress JN, Childs ML, De Leo GA, Kirk DG, MacDonald AJ, Olivarius K, Pickel DG, Roberts SO, Winokur OC, Young HS, Cheng J, Grant EA, Kurzner PM, Kyaw S, Lin BJ, Lopez RC, Massihpour DS, Olsen EC, Roache M, Ruiz A, Schultz EA, Shafat M, Spencer RL, Bharti N, Mordecai EA. The influence of vector-borne disease on human history: socio-ecological mechanisms. Ecol Lett. 2021 Apr;24(4):829-846. National Academies of Sciences, Engineering, and Medicine 2016. Global Health Impacts of Vector-Borne Diseases: Workshop Summary. Washington, DC: The National Academies Press. https://doi.org/10.17226/21792.

[9] Dye-Braumuller KC, Kanyangarara M. Malaria in the USA: How Vulnerable Are We to Future Outbreaks? Curr Trop Med Rep. 2021;8(1):43-51. doi: 10.1007/s40475-020-00224-z. Over half of known human pathogenic diseases can be aggravated by climate change, Aug. 8, 2022, https://www.nature.com/articles/s41558-022-01426-1; https://www.lshtm.ac.uk/newsevents/news/2021/malaria-and-dengue-predicted-affect-billions-more-people-if-global-warming

[10] https://obamawhitehouse.archives.gov/the-press-office/2016/02/08/fact-sheet-preparing-and-responding-zika-virus-home-and-abroad; Sarkar, S., Gardner, L. Zika: the cost of neglect. Palgrave Commun **2**, 16060 (2016). https://doi.org/10.1057/palcomms.2016.60

[11] https://www.cdc.gov/vhf/ebola/history/2014-2016-outbreak/index.html; https://www.cdc.gov/media/releases/2019/p0717-ebola.html

[12] https://www.kff.org/global-health-policy/fact-sheet/the-u-s-government-and-global-health/

[13] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/neglected-tropical-diseases-developing-world-developing-drugs-treatment-or-prevention

B. **Consider including behavioral health research among 'warm base' clinical research activities and using Community Mental Health Centers (CMHCs), Substance Use Treatment Centers, Certified Community Behavioral Health Clinics (CCBHCs) and Opioid Treatment Centers as potential study sites**: About 14.5 percent of US adults 12 years and older had a substance use disorder in 2020 and 21 percent of US adults age 18 and older had a(ny) mental illness.[14] According to the World Health Organization's 2022 World Mental Health Report, nearly 1 billion people have a mental health condition.[15] Along with heart disease and cancer, mental health conditions and substance use disorders could be a subject of 'warm base' clinical research of interest to communities. As with many NTDs, both WHO and US agencies have noted persons with behavioral health conditions encounter significant stigma and discrimination and underserved populations (those with lower income, homeless persons, racial and ethnic minorities, indigenous persons) face increased risks relative to the general population.[16]

Like federally qualified health centers and retail pharmacy chains, noted under the RFI heading of Identifying and Incentivizing Research Institutions and Networks; Building Diversity and Equity as potential study sites, behavioral health facilities, subject to appropriate ethical review (heightened as psychiatric populations may be more vulnerable than others to coercion, etc.), could serve as clinical research sites for psychiatric and behavioral health treatment studies.[17] There are roughly 16000 substance use treatment facilities, 12300 mental health treatment facilities and 1900 opioid treatment programs.[18] CCBHCs and CMHCs are among these providers, are distinct and provide specialized services.[19] Among behavioral health facilities, CCBHCs and CMHCs often receive federal funding and could be well-suited for the type of 'warm base' research contemplated by the RFI.

C. **Focus on drug repurposing/repositioning**: an ideal purpose for the governance model, emergency master agreement and 'warm base' research may be to consider how best to support and implement drug repurposing studies for NTDs, agents noted in the National Biodefense Strategy[20] and agents of concern identified by CDC.[21] Drug repurposing-developing "new uses for approved or investigational drugs that are outside the scope of the original medical indication"[22] garnered significant interest during the COVID-19 public health emergency though not all agents evaluated ultimately proved safe and effective. FDA, the Reagan-Udall Foundation and NIH recently held a workshop on drug repurposing and several

[14] https://www.samhsa.gov/data/release/2020-national-survey-drug-use-and-health-nsduh-releases
[15] https://www.who.int/publications/i/item/9789240049338
[16] Id.; https://unitedgmh.org/knowledge-hub/uhc/; https://www.samhsa.gov/behavioral-health-equity/obhe-data
[17] https://www.samhsa.gov/newsroom/press-announcements/202109281153; https://www.thenationalcouncil.org/program/ccbhc-success-center/ccbhc-overview/; Tcheremissine OV, Rossman WE, Castro MA, Gardner DR. Conducting clinical research in community mental health settings: Opportunities and challenges. World J Psychiatry. 2014 Sep 22;4(3):49-55; https://med.umn.edu/news-events/first-human-clinical-trial-vaccine-treat-opioid-use-disorders-enrolls-first-patients; https://www.samhsa.gov/medication-assisted-treatment/become-accredited-opioid-treatment-program; Carlson C, Sweetland A, Wainberg M. Ethical challenges in global mental health clinical trials. Lancet Psychiatry. 2018 Nov;5(11):866-867. doi: 10.1016/S2215-0366(18)30300-6
[18] https://www.samhsa.gov/data/report/national-survey-substance-abuse-treatment-services-n-ssats-2020-data-substance-abuse; https://www.samhsa.gov/data/report/national-mental-health-services-survey-n-mhss-2020-data-mental-health-treatment-facilities; https://www.aatod.org/increasing-the-number-of-otps-and-patients-in-the-united-states/; https://www.aatod.org/increasing-the-number-of-otps-and-patients-in-the-united-states/
[19] Wishon AA, Brown JD. Differences in Services Offered by Certified Community Behavioral Health Clinics and Community Mental Health Centers. Psychiatr Serv. 2022 Sep 13:appips20220211. doi: 10.1176/appi.ps.20220211.
[20] https://www.whitehouse.gov/briefing-room/statements-releases/2022/10/18/fact-sheet-biden-harris-administration-releases-strategy-to-strengthen-health-security-and-prepare-for-biothreats/
[21] https://emergency.cdc.gov/agent/agentlist-category.asp
[22] Pushpakom S, Iorio F, Eyers PA, Escott KJ, Hopper S, Wells A, Doig A, Guilliams T, Latimer J, McNamee C, Norris A, Sanseau P, Cavalla D, Pirmohamed M. Drug repurposing: progress, challenges and recommendations. Nat Rev Drug Discov. 2019 Jan;18(1):41-58. doi: 10.1038/nrd.2018.168

organizations such as Cures Within Reach support these efforts.[23] Developing research protocols and agreements about such studies even before an epidemic or pandemic and supporting a network of researchers whether through 'warm base' research or other means could be a major contribution of OSTP's efforts.[24] While most repurposing focus is on pharmaceutical products, medical devices and biological products also could be included. For instance, vaccines intended for smallpox were successfully used to treat the Monkeypox (MPOX) Virus.[25]

Sincerely,

Mitchell Berger, Comment Submitted 11.27.22: mazruia@hotmail.com

Note: Please note that I am a federal/HHS employee. However, I am submitting these suggestions in my personal/private capacity. The views expressed are mine only and should not be imputed to other individuals nor to any public or private entity.

[23] https://clue.io/repurposing; https://reaganudall.org/news-and-events/events/repurposing-patent-drugs-research-regulatory-challenges; https://www.cureswithinreach.org/

[24] Chakraborty C, Sharma AR, Bhattacharya M, Agoramoorthy G, Lee SS. The Drug Repurposing for COVID-19 Clinical Trials Provide Very Effective Therapeutic Combinations: Lessons Learned From Major Clinical Studies. Front Pharmacol. 2021 Nov 18;12:704205. Begley CG et. al. Drug repurposing: Misconceptions, challenges, and opportunities for academic researchers. Sci Transl Med. 2021 Sep 22;13(612):eabd5524. doi: 10.1126/scitranslmed.abd5524

[25] Islam MR, Hossain MJ, Roy A, Hasan AHMN, Rahman MA, Shahriar M, Bhuiyan MA. Repositioning potentials of smallpox vaccines and antiviral agents in monkeypox outbreak: A rapid review on comparative benefits and risks. Health Sci Rep. 2022 Aug 23;5(5):e798; https://www.who.int/news-room/fact-sheets/detail/monkeypox

Hello,

Thank you for sending out this RFI.

I am a physician-scientist with national expertise in drug and vaccine allergy who was involved during the pandemic in vaccine safety research. I was particularly involved the safety of the mRNA COVID vaccines and whether or not the excipient polyethylene glycol did or did not need to be implicated as a reagent that could cause immediate hypersensitivity reactions. There were a few thoughts that I wanted to put forth on the topic of warm base research.

The issue that arose in December 2020 was that with the rollout of the vaccines, people reported some rare immediate hypersensitivity reactions (things like hives, swelling, anaphylaxis, etc.) to those vaccines, which was then used by vaccine skeptics as an excuse not to get vaccinated. These reactions needed to be rapidly investigated to understand a few key points: 1. Could someone who reacted be safely immunized with a subsequent dose, and 2. what was the underlying mechanism of these reactions. We, among others worked rapidly to create multicenter collaborations using similar testing and evaluation protocols, and as a result, we were able to provide hypothesis driven research that helped to answer both of those questions, at least to the degree possible, but the ball of skepticism was already rolling very quickly by then. Despite being very effective vaccines that reduced mortality and morbidity dramatically, the first use of mRNA vaccines wrapped in the first use of liposomal carriers containing PEG 2000 as a vehicle was too much for a lot of skeptical people to swallow.

I can see that for the future, there could be a much better way to approach this, and it would be to 1. understand the potential allergenicity, or not, of key ingredients that would be used in a standardized way across all vaccines, prior to implementing them, and 2. to have a national system of clinical expertise for rapidly evaluating adverse vaccine reactions and deciding when to reimmunize someone, and 3. to better understand and try to improve upon the disproportionate reporting of adverse vaccine reactions in women.

1. **An area of warm safety research prior to a future pandemic would therefore be to work on the issue of allergenicity of key vaccine ingredients prior to their use, to try and know beforehand whether a vaccine would be safe for people with certain allergies, and ideally to avoid using ingredients that might have a widespread allergenicity.**
    a. Some key allergens to avoid being egg, gelatin, alpha-gal, and high molecular weight polyethylene glycol. I think we got lucky in that PEG 2000 is short enough of a molecule that even many truly PEG allergic patients were able to be safely immunized. They typically react severely at a threshold starting with a molecular weight of PEG 3350.
    b. Key studies that would be of value to perform would be to validate assays for allergen detection across key vaccines as a quality control. i.e. we measure whether or not there is "egg" in this vaccine.

        i. I believe that this can be done going forward, either by using current techniques from patient serum or from monoclonal antibody technologies.
    c. And to validate whether vaccines which must contain specific ingredients due to a crucial role for that ingredient in the vaccine's function can still be safely used (or not) in patients who have that specific allergy.
2. **Another area of warm safety research would be the establishment of centers of excellence for vaccine safety in patients who have experienced a previous adverse vaccine reaction, or perceive themself to be at increased risk of an adverse event due to other allergies. Patients would know that they are able to get a complete evaluation for their problem, contribute to studies of their particular adverse reaction, and there would be scientists who are trying to unravel "why did this happen to you when it didn't happen to anyone else?"**
    a. This would be different from the CDC's CISA network, I think, and complementary to it, potentially functioning as the clinical allergy spokes in a wheel where CISA is at the hub. The goal would be that patients would be able to be directly tested for a problem and subsequently immunized as often as possible by an evaluating allergy physician when the problem of concern has been disproven as a major safety issue.
    b. This system would also be able to rapidly flex and create multi-center research to identify and resolve problems that might occur too rarely at any one institution for people to compare notes, or would overwhelm a centralized system when it needs to have lots of clinicians spready widely to cover enough ground.
    c. This system would also be able to function as clinical trial sites for recruiting specific patient populations who might be hesitant about a specific vaccine's safety profile related to their specific health problem. Clinicians who serve as site leads would also be trained and provided effort as clinical research PIs using standardized protocols when their services were needed.
        i. This type of hub and spoke system is needed for vaccine safety trials in specialized populations, because patients with specific health problems (especially those of the immune system or allergy) do not participate in clinical trials of vaccine safety at the same rate as healthy individuals, and they might not believe that the results of a clinical trial would not apply to them.
        ii. This type of hub and spoke system is needed for vaccine safety trials in specialized populations, because allergy physicians are highly trained in managing adverse reactions when they do arise, and our patients are often unwilling to be immunized in a general setting until we can assuage their concerns. However, they are willing to be immunized under our observation.

3. **Another key area of warm safety research prior to a future pandemic is the question of why vaccine adverse events are disproportionately experienced and reported by women overall. This has been an unanswered question for decades. Women**

typically comprise 80% of adverse vaccine reactors across all vaccines that are available to the general public, which may suggest that their immune responses are somewhat different from men or that they may need dose adjustments.

a. Further, women need special attention and study due to the need to understand the safety of key vaccines during pregnancy and lactation.

I believe that a national multi-site program with a hub and spoke design where the spokes were comprised of centers of clinical excellence in vaccine allergy evaluation, research and management could serve the nation well in pandemic times. Such as system would be able to rapidly activate, scale up, study, and address real or perceived patient concerns related to vaccine allergy and adverse events, in addition to supporting other types of clinical trials. During non-pandemic times, such as system would also function as a network for monitoring, evaluating, and studying the safety of routine immunizations and improving the public's perception of their utility.

I hope that I have been on topic to your request. Thank you for seeking feedback! I am happy to provide references to publications that support my points or verify my expertise on this topic.

Sincerely,

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RFI; Clinical Research Infrastructure and Emergency Clinical Trials

Prepared by: Gav Martell, YonaLink Inc
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416-662-5074

December 27, 2022

Gav Martell, the respondent, is co-founder and VP of Business Development of YonaLink Inc, a company established in the state of Delaware, with offices in Boston, MA. YonaLink is a company that provides software as a service for clinical trials. Specifically:

1) As a platform to stream data from Medical Center EHRs (Electronic Health Records) and other eSources to the trial EDC (Electronic Data Capture system)
2) Provides a next generation EDC system that was built specifically with data streaming in mind, including all the workflow and tools necessary to stream data from multiple sources into the EDC

Comment:

The challenges that are outlines in this RFI are not new to clinical trials. Issues related to the interoperability of health systems is at the core of challenges that prevent technological solutions from coming to market in an efficient and scalable way. From a clinical trials perspective specifically, the FDA has recognized the inherent advantage that could be realized if this technological barrier could be solved. In 2018 the FDA published their "Guidance for the Industry: Use of Electronic Health Record Data in Clinical Investigations" (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/use-electronic-health-record-data-clinical-investigations-guidance-industry). Specifically, it outlines "Interoperable systems simplify data collection for a clinical investigation by enabling clinical investigators and study personnel to capture source data at the patient's point-of-care visit. Interoperable systems may also reduce errors in data transcription, allowing for the improvement in data accuracy and the quality and efficiency of the data collected in clinical investigations" (page 5). Ultimately, the interoperability of systems remains the biggest hurdle to solve this problem.

With this in mind, it is our belief that the U.S. government would be best served to function in a capacity to oversee the development of emergency clinical trial protocols, in coordination with stakeholders external to the U.S. government. Whether trials in emergency settings are simple or complex, ultimately the best route to a dynamic, and prepared solution, is one that leverages the systems and infrastructure already in place. In the case of an emergency, these systems could be leveraged to quickly and effectively have clinical trials up and running, with little to no barriers impeding setup and execution. Sites would not be required to learn new systems or put new and untested solutions or protocols in place, and the US Government would not be required to reproduce workflow, processes and systems that are already proven.

To achieve this goal, the US Government would be best served to put together a consortium of sites willing to participate, software system vendors (EHR-to-EDC service provider, data analytics etc.), and US-based pharma companies.

This group could work together on several levels:

1) To help establish policies and procedures for emergency outbreak response, including emergency trials
2) Run real-world clinical trials within the existing network of medical sites to ensure preparedness of the systems and protocols in place should an emergency trial be required – aka a "warm base"
3) Provide feedback to the U.S. Government on the readiness of such systems and solutions for their effective use in an emergency situation.
4) Create a framework for an "Emergency Master Agreement"

Systems, such as YonaLink, which was uniquely built to overcome the interoperability issues at the site level and overcomes the challenge of integrating with the sites themselves in order to stream patient data from the EHRs to the EDC, exist today. Structured data can be streamed from 30,000+ medical centers in the United States, and data can be pooled from all of these patients and sites into a central EDC. By significantly reducing the amount of data that needs to be manually copied from site EHRs, to the EDC, the barrier for medical sites to participate in clinical trials is significantly reduced. If thousands and thousands of the data points can be streamed from EHR-to-EDC, the burden on site staff is minimalized. This allows locations who previously did not have sufficient staff to manage clinical trials to now be active trial sites. This would increase the ability of smaller medical centers and sites to participate in clinical trials, while also expanding the pool of patients who can participate in them. This in turn increases the diversity of the eligible population. Interested institutions and networks can be invited to participate in this consortium, and emergency preparedness. By running clinical trials, in a non-emergency environment, within this consortium, the advantages are self-evident:

- Pharma companies have an expanded network of sites in which to conduct trials and expand their patient pool for clinical trials, increasing diversity
- the emergency preparedness levels are improved because the system is being constantly tested in a real-world environment
- sites are incentivized to participate as they generate revenues from the "warm base" trials, and future potential revenues from emergency clinical trials

By lowering the barrier for smaller medical sites to participate in this consortium, it ensures that trial sites in underserved areas are included, and likewise increases the diversity both among study participants and among the investigators who lead trials to completion.

Sites that have implemented a FHIR-based interface as outlined in the 21st Century Cures Act (US or internationally based) would be eligible to participate. In addition, international sites could provide a similar integration that would allow for EHR-to-EDC data streaming, and that could be defined within the boundary of this Emergency Preparedness Consortium. For example, a recent grant was award in Israel by the Israeli Innovation Authority that specifically encourages the majority of medical centers to provide technically integrated solutions for clinical trials. In just a year's time, any clinical trial in Israel will be able to stream data from the EHR of any patient, to a nation-wide EDC. Thus, opening up Israel to an increasing pool of clinical trials. If mass amounts of data can be streamed from the sites to the sponsors, why would anyone pay to have it manually copied any longer? Such networks in Israel or elsewhere can easily join a system such as the one proposed by the U.S. Government.

We would definitely agree that in advance of an outbreak or other emergency, there is value in having networks and sites carrying out clinical trials to create a "warm base" of clinical research capacity. It should be a measured goal of the consortium to have a "warm base" that continually tests and refines the procedures which enhances U.S. clinical trial capacity overall while also enlarging the network of sites that can be available to carry out emergency clinical trial research when the need arises. Pharma companies would ultimately be called upon to provide these warm trials, with the incentive, that in an emergency situation, they will also be called upon by the U.S. Government to run trials as it relates to critical vaccines or therapies needed. By running "warm base" trials, a key measure would be an increase in the diversity among clinical trial participants and among investigators, and also of increasing capacity for clinical research in underserved areas. If an emergency response system is going to be scalable and worthwhile, it must be able to expand beyond the current system of large medical centers in major U.S. metropolises, and continue to include small to mid-sized medical centers as well. This provides the necessary impetus at all levels (industry, government, patient, etc) to expand clinical trials into new communities and locations that today are underserved. The "warm base" at its essence is opening new doors by bringing clinical trials to areas which today are not represented.

January 27, 2023

White House Office of Science and Technology Policy emergencyclinicaltrials@ostp.eop.gov

Re: Request for Information; Clinical Research Infrastructure and Emergency Clinical Trials

To whom it may concern,

Genentech, a member of the Roche Group, thanks the White House Office of Science and Technology Policy (OSTP) for the opportunity to submit comments in response to the Request for Information (RFI) on Clinical Research Infrastructure and Emergency Clinical Trials. We applaud OSTP's efforts to ensure that coordinated and large-scale clinical trials can be efficiently carried out across a range of institutions and sites to address outbreaks of disease and other emergencies.

We acknowledge the ask for potential governance models for the emergency clinical trials effort, specifically the approach of including a centralized U.S.-level structure drawing membership from Federal agencies with relevant expertise. Genentech believes that appropriate stakeholders including the biopharmaceutical sector could unite to create an advisory committee similar to the CDC's Advisory Committee on Immunization Practices (ACIP), the Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria (PACCARB), and the National Vaccine Advisory Committee (NVAC). We believe that merely requiring consultation between agencies is insufficient to resolve key challenges to proactively prepare for future pandemics; instead we urge OSTP to consider enhancing coordination between the sub-agencies at the Department of Health and Human Services (HHS) and liaise with OSTP. Delineating accountabilities of each agency and replacing consultation between agencies with a cross agency body and centralized coordinator will help to avoid potentially redundant programs, efficiently allocate resources, and clarify decision making for its partners and the public.

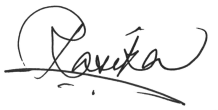
Centralizing the coordination of programs would not be possible without the support and expertise of stakeholders across the clinical trial lifecycle. We would like to highlight Genentech's External Council for Inclusive Research, which relies on guidance from physician thought leaders, academic research experts, and patient advocates to evaluate and make changes to our clinical trial processes, such as modifying clinical trial protocol design and expectations for research collaborators. Using this model, public health agencies could similarly seek input on enhancing support and proactively planning for the needs of vulnerable and underserved populations.

Genentech appreciates OSTP's acknowledgement of the need to invest in modernizing clinical research, and believe flexibilities and lessons learned through this pandemic provide a foundation on which to build a resilient national infrastructure for clinical trials of the future. The use of digital technologies, including telehealth and remote monitoring devices, as well as other flexibilities afforded by regulatory agencies such as remote data capture, rapid protocol amendment, etc., proved critical to the continued participation of patients in clinical trials during the pandemic, and allowed important research to continue. Outside of the pandemic context, digital technologies and broader use of decentralized trial designs could address the historical underrepresentation of minority and other patient groups in clinical research. We acknowledge, however, that as we expand digital means to collect information, there is potential for digital technologies to widen the gap if tools (e.g. iPads, phones, stable internet access) are not available in rural communities or in families with lower socioeconomic status - technology itself is not a standalone solution but should be bolstered by social context.

While we appreciated regulatory flexibilities offered by individual health authorities during the pandemic, as a sponsor of global clinical studies, we derived maximum benefit from flexibilities that were harmonized across multiple jurisdictions. Thus, we strongly support harmonization of regulatory

policies and action across global health authorities, as such coordination reduces conflicting or redundant work, resulting in less time and cost to bring treatments to patients. We would like to thank White House Office of Science and Technology Policy for the opportunity to comment on this important request for information. Should OSTP have questions on any of these points, we would be happy to provide additional clarification.

Sincerely,



Rasika Kalamegham
Head, US Regulatory Policy
Genentech Inc.

Jill Shotzberger
Senior Director, Federal Government Affairs
Genentech Inc.

Section/Text Reference	*Comment/Recommendation*
1. *Governance for emergency clinical trials response.* *a.* Descriptions of models that could be used to establish a U.S.-level governance structure for emergency clinical trials. As noted above, one possible approach would be a centralized U.S.-level structure drawing membership from Federal agencies with relevant expertise.	The biopharmaceutical industry, supply and distribution leaders and state, local, tribal and public health leaders are just a few of the groups that could unite to create an advisory committee similar to the CDC's Advisory Committee on Immunization Practices (ACIP), the Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria (PACCARB), and the National Vaccine Advisory Committee (NVAC). This stakeholder advisory board could provide expertise and input to the cross agency body as well as appropriate sub agencies on how to better engage with the private sector on topics like: ● Strategic portfolio management, ● How to best work with industry to anticipate, prepare, scale-up and "right-size" for a surge, ● Leverage appropriate and novel technologies for development and manufacturing, securing the supply chain, and optimizing deployment of medical countermeasures (MCMs). ● Centralized communication which incorporates patient engagement and dissemination of information about available clinical trials in various communities, e.g. the central coordinating body could develop a portal and language that can then be used by local and community doctors, leveraging existing trusted persons and/or institutions. The engagement of this advisory board could help our response agencies do what they must do – move at the speed of science to prepare and respond to emergencies of all types.
1. *Governance for emergency clinical trials response.* *f.* Procedures whereby the U.S. Government, together with external	Collectively, HHS and its sub-agencies are essential in spearheading the government's basic, clinical, epidemiological, behavioral, and translational research. Administration for Strategic Preparedness and Response (ASPR) and BARDA also demonstrated their leadership in partnering with the private sector to conduct advanced research, expand manufacturing capacity and deploy resources in a time of crisis. However, determining what agency was accountable for specific activities and which group had available funding to pursue these efforts often led to delay and confusion during the COVID-19

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stakeholders, could oversee the development of clinical trial protocols and, where appropriate, the selection of investigational agents. It would be particularly helpful to get input on whether there is a role for public-private partnerships in this context.	PHE. We are concerned that merely requiring consultation between agencies is insufficient to resolve these key challenges to proactively prepare for future pandemics. We therefore urge consideration on the following points: 1. The newly created White House Office of Pandemic Preparedness and Response Policy (as part of the end of year omnibus package (sec. 2104) is responsible for the development and implementation of the national biodefense strategy - we believe the office should seek input from industry on the plan. 2. There is also an opportunity for the newly created White House Office of Pandemic Preparedness and Response Policy to create centers of excellence, overseen by a cross agency counsel and the designated preparedness and response coordinator to delineate responsibilities and accountabilities of each agency to avoid potentially redundant programs, efficiently allocate resources, and clarify decision making for its partners and the public. 3. Throughout the COVID-19 PHE, BARDA has not only partnered to deploy and scale manufacturing capabilities, but overseen complex advanced research projects to deliver next generation MCMs. To effectively manage the lifecycle of MCM discovery, development and sustainable procurement, BARDA and programs like BioShield must be adequately resourced and delegated the necessary authority to enable the availability of MCMs in advance of when a public health threat emerges.
2. *Identifying and Incentivizing Research Institutions and Networks; Building Diversity and Equity.*	Several years ago, Genentech established its Advancing Inclusive Research (AIR) initiative, a U.S.-focused and cross-organizational effort that ensures clinical research participants are representative of broad patient populations. Because disease outcomes and drug responses can vary across populations, research must include patients who are racially, ethnically, and gender representative of those who experience disease. We are deeply committed to addressing barriers to clinical trial participation, diversifying genetic data for scientific discovery, and increasing access to innovative diagnostic and therapeutic solutions, by advancing inclusive research. Under this initiative, we created an External Council for Inclusive Research, which includes physician thought leaders, academic research experts, and patient advocates. Based on their guidance, we evaluated and made changes to our clinical trial processes, such as modifying clinical trial protocol design and expectations for research collaborators. Using this model, public health agencies could similarly seek input on enhancing support and proactively planning for the needs of vulnerable populations. Genentech also leads a coalition of clinical research centers that are exploring how to build a sustainable ecosystem that facilitates the inclusion of historically underrepresented people in all clinical research.[1] Together, we

[1] https://www.gene.com/stories/pursuing-a-new-paradigm-in-inclusive-research. Inaugural partners include Mays Cancer Center, home to UT Health San Antonio MD Anderson, San Antonio, Texas; O'Neal Comprehensive Cancer Center, University of Alabama at Birmingham, Birmingham, Alabama; and West Cancer Center, Memphis, Tennessee.

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	aim to advance the participation of diverse patient populations in our clinical trials, test recruitment and retention approaches, and establish best practices that can be leveraged across the industry and other disease areas to help achieve health equity for all people. The Biomedical Advanced Research and Development Authority (BARDA) played a critical role in advancing this work during the COVID-19 public health emergency (PHE). Using the Other Transaction Agreements (OTA) framework, Genentech and BARDA rapidly partnered to evaluate use of Actemra (tocilizumab) in patients with severe COVID-19. The resulting COVACTA trial was vital because there were no well-controlled studies and limited published evidence on the safety or efficacy of Actemra in the treatment of those patients.[2] Because of the speed and success of COVACTA, Genentech was able to initiate a second Phase III study in EMPACTA, that focused on enrolling patients at trial sites known to provide critical care to underserved and minority populations that often do not have access to clinical trials.[3] Partnership with BARDA is an important example of how the U.S. government, private industry like Genentech, and health care communities can successfully partner on advanced research to serve disproportionately impacted populations, even and especially in the midst of a PHE.
2. *Identifying and Incentivizing Research Institutions and Networks; Building Diversity and Equity.* a. Methods for identifying institutions and sites that may have an existing interest in or familiarity with emergency clinical trial research. This might include those that currently receive government funding, those with a focus on infectious disease research, and/or those that have worked with CROs. Methods for identifying institutions and sites that may have an	We recommend U.S. Government agencies enact the following activities: ● Put in place immediate SWAT cross-functional team to work with outside providers to manage protocol design & writing and study set up including accounting for potential protocol deviations. The team could proactively identify how data captured in an emergency clinical trial setting could be assessed for regulatory decision-making purposes given that these studies will often have incomplete or limited data. Guidance or uniform standards determined with stakeholder input could enhance the ability of sites and sponsors to be nimble in efficient execution of clinical trials. ● Lessons learned from assessments of Covid-19 studies should be shared both within government and beyond i.e. academic medical centers, CROs, sponsors etc. such that each stakeholder is aware of complexities in conduct of clinical trials, critical attributes that can hamper assessment of final data package and flexibilities that can be adopted to ameliorate emergency situations. ● Recommend CROs have a process in place to manage trials that see patients via emergency room (i.e. Acute care setting). ● Ensure sponsor SWAT team is multi-disciplinary, which would include drug supply team members. OSTP may need to consider the use of commercial drugs not labeled for clinical trials (for speed purposes), so the Office would in turn need steps to ensure sponsor accountability on how to move forward with use. ● Given the infectious disease situation and a new pandemic with lack of knowledge on how to manage early, we recommend that U.S.

[2] *A Study to Evaluate the Safety and Efficacy of Tocilizumab in Patients With Severe COVID-19 Pneumonia (COVACTA)*, ClinicalTrials.gov Identifier: NCT04320615, https://clinicaltrials.gov/ct2/show/NCT04320615

[3] *A Study to Evaluate the Efficacy and Safety of Tocilizumab in Hospitalized Participants With COVID-19 Pneumonia (EMPACTA)*, ClinicalTrials.gov Identifier: NCT04320615, https://clinicaltrials.gov/ct2/show/NCT04372186.

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existing interest in or familiarity with emergency clinical trial research. This might include those that currently receive government funding, those with a focus on infectious disease research, and/or those that have worked with CROs.	Government agencies allow and document alternative processes that may help manage an ER situation ○ For example, flexibility in equipment/testing requirements and oversight capability for community institution participation in trials not limited to just ER settings. ● Clear instructions on data capture such that it will be accepted by FDA . We urge the OSTP to coordinate with FDA and build on the flexibilities offered during the PHE i.e. allowing the use of remote monitoring devices for data capture in a clinical trial, allowing protocol deviations and amendments to respond to geographical surges in infection rates, leveraging use of real world evidence (RWE) for regulatory decision making etc.
2. *Identifying and Incentivizing Research Institutions and Networks; Building Diversity and Equity.* b. Effective ways to increase diversity among study participants and investigators, and to expand clinical research sites into underserved areas. It would be helpful to get input on whether and how the following approaches could be useful: ii. Use of decentralized clinical trial (DCT) design elementse. iii. Use of technological innovations, such as digital health technologies (DHTs)	We appreciate OSTP's acknowledgement of the need to modernize clinical research, and believe flexibilities and lessons learned through this pandemic provide a foundation on which to build. One notable example is the regulatory flexibility granted by FDA to support the ongoing conduct of "hybrid" trials that leveraged both remote and in-person consultations where possible. The use of digital technologies, including telehealth and remote monitoring devices, proved critical to the continued participation of patients in these trials, and allowed important research to continue. Outside of the pandemic context, digital technologies and broader use of decentralized trial designs can also help address the historical underrepresentation of minority and other patient groups in clinical research. We support engaging with the FDA to encourage and increase use of such flexibilities during and beyond PHEs. We note that although the recently passed PDUFA VII law contains provisions for FDA to issue guidances addressing some of these topics, there is value in engaging with the Agency on how these flexibilities can particularly be leveraged during a PHE. We strongly support harmonization of regulatory policy and action across reputable global health authorities - particularly with respect to manufacturing and inspections , as such coordination reduces conflicting or redundant work, resulting in less time and cost to bring treatments to patients. We encourage OSTP to work with FDA to explore expanded use of mutual recognition and mutual inspection reliance agreements, which currently are limited in scope. Additionally, we believe FDA and other regulatory bodies should continue to engage with their counterparts internationally and play a leading role in the ICMRA Manufacturing Covid-19 lessons learned activities, to support future global responses and alignment. These engagements are a valuable tool to exchange best practises and learn from each other- especially when there are local/regional variations or limitations to implementation. These are also great venues to encourage harmonization of guidelines and policies that can be applied consistently and globally.
2. *Identifying and Incentivizing Research*	We share the commitment to using DCT approaches to expand access to studies especially to underserved populations. However, in order to

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Institutions and Networks; Building Diversity and Equity. b. Effective ways to increase diversity among study participants and investigators, and to expand clinical research sites into underserved areas. It would be helpful to get input on whether and how the following approaches could be useful: ii. Use of decentralized clinical trial (DCT) design elements	implement these methods, we seek clarity from appropriate Federal agencies on specific challenges including methods for ascertaining remote consent, patient privacy considerations, and appropriate handling of data collected directly by the trial sponsor remotely. We seek clear instructions on data capture such that it will be accepted by FDA . We urge the OSTP to coordinate with FDA and build on the flexibilities offered during the PHE i.e. allowing the use of remote monitoring devices for data capture in a clinical trial, allowing protocol deviations and amendments to respond to geographical surges in infection rates, leveraging use of real world evidence (RWE) for regulatory decisionmaking etc. Further, we encourage leveraging the strengths and capabilities of the Office of the National Coordinator (ONC) in establishing working groups that can set standards for data capture, transmission and collation using various tools and platforms. Given the importance of clinical staff diversity, we recommend collaborating with ACRP who is building short programs to grow the number and diversity of research coordinator professions such as study coordinators, navigators and other patient facing staff. We also recommend considering a framework for the recruitment of investigators who are multilingual or have established ties to local communities beyond the hospital setting. We also recommend CROs have a process in place to manage trials that see patients via emergency room (i.e. Acute care setting).
2. *Identifying and Incentivizing Research Institutions and Networks; Building Diversity and Equity.* b. Effective ways to increase diversity among study participants and investigators, and to expand clinical research sites into underserved areas. It would be helpful to get input on whether and how the following approaches could be useful: ii. Use of decentralized clinical trial (DCT) design	Currently, state medical licensure disparities can be limiting implementation of decentralized clinical trials (DCTs). The putative advantage of a DCT design is enabling an investigator to work with a patient regardless of location. Thus, limiting investigators to work with patients only in a specific state negates the promise of a DCT. Medical licensure is regulated at the state level, but investigational clinical trials and their conduct are regulated at the federal level. State licensure requirements can place a barrier on decentralized clinical trials, as it would need investigators that are licensed in all 50 states. In response to the COVID 19 crisis, many states temporarily modified licensure requirements for health care providers, including out-of-state requirements for telehealth. Note however, that the flexibilities were only extended to telehealth consultations for routine care and not for clinical trials. The successful uptake of telehealth by both patients and providers suggests that it can be employed at scale for clinical trial evaluations as well. Flexible reciprocity schemes, such as the Interstate Medical Licensure Compact, can facilitate the running of trials across multiple states. Additionally, federal and state legislation that would ease or remove these licensure barriers and/or differentiate the practice of medicine and clinical trials (e.g., limited waivers could be created for clinical trials) would have a positive impact. We note that one of the key challenges for patients participating in clinical trails is the requirement for in-person site visits. If we are able to leverage

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elements, or other innovative approaches such as trials conducted at the point of care.	remote monitoring approaches (e.g. telehealth evaluations) to reduce in-person site visits, we may be able to attract and retain patients in clinical trials. Remote monitoring and DCT approaches could also make clinical trials accessible to patients who are physically remote from traditional clinical trial sites which tend to be in urban centers. Thus, these approaches could make trials more attractive to rural and remote populations which also tend to be underserved and underrepresented.
4. Emergency Master Agreement. a. Basic terms that might form part of an Emergency Master Agreement, including the following. iii. *Use of a single IRB* across all participating trial sites. As a related point, it would be helpful to get feedback on whether an IRB should be established that is primarily devoted to emergency clinical trials.	Clinical trial and site start-up hurdles & delays remain a universal issue. We encourage OSTP to convene a taskforce to understand why central IRBs are not the norm despite urging from multiple stakeholders to be adopted. The National Academies of Sciences, Engineering, and Medicine report[4] and the NIH report[5] on IRBs remain existing bodies of work that have not been implemented. We encourage OSTP to specifically assess why the following suggestions are not being universally adopted and offer to work with OSTP to address hurdles to adoption: ● Urge sites to use central IRB (vs local IRB) to speed up study initiation ● Use of Attestation to allow work at risk while negotiating contract (Modified process) ● Recommend that sites/institutions have a modified process in place to manage in an Emergency Room (ER) (acute care) component Overall, we are not in favor of establishing an IRB that is primarily devoted to emergency clinical trials, but rather a centralized IRB that has extensive experience in both emergency and non-emergency situations and leverages existing work so they are efficient, experienced and impactful.
5. *Identifying viable technical strategies for data capture; gathering information about a potential data capture pilot.*	The use of digital technologies and advancement of new analytical approaches have facilitated the generation and analysis of vast healthcare data. These data are accruing exponentially and can offer insights that accelerate the development of new treatments, as well as our understanding of how they work outside the clinical setting. The 21st Century Cures Act focused on the use of these types of data to support regulatory decision-making and yet while progress has been made, much more can be done. We strongly support the continued emphasis on the use of real-world data and evidence (RWD, RWE) to support regulatory decision-making, and encourage the committee to include accountabilities within FDA to swiftly and substantially facilitate such use of these data. In addition we point to the recently passed PDUFA VII reauthorization which will allow FDA to modernize its IT infrastructure to enable cloud-based

[4] Institute of Medicine. 2000. *Institutional Review Boards and Health Services Research Data Privacy: A Workshop Summary*. Washington, DC: The National Academies Press. https://doi.org/10.17226/9890.

[5] Grady C. Institutional Review Boards: Purpose and Challenges. Chest. 2015 Nov;148(5):1148-1155. doi: 10.1378/chest.15-0706. PMID: 26042632; PMCID: PMC4631034.

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	submission of regulatory data. This is an important step to streamline data capture and submission. We can envision a future state wherein data is captured via a wearable and directly uploaded to the cloud such that both the sponsor and regulator have immediate access to the raw data. This will eventually enable simultaneous and real time assessment of study results ultimately speeding the conduct and regulatory evaluation of clinical trials.
5. *Identifying viable technical strategies for data capture; gathering information about a potential data capture pilot.*	The FDA is seen as a trusted source of information by key stakeholders in drug development and by the public. While the Agency's website provides a vast amount of information, the organization of information could be improved. For example, most informational pages on the website seem to have been written and updated by a specific Center/Division. Some of these pages provide excellent, well-organized information; however, the publication of a page by just one center or division creates ambiguity about whether the statements made are endorsed by the other centers/divisions and/or the Agency as a whole. The information often appears siloed with some topics covered on different pages across different centers. We fully support the Agency's efforts to improve the accessibility of important drug-related information for patients and their families and consequently recommend FDA take steps to ensure information is provided to all patients at the site of care - this will help to improve participation within underserved communities and mitigate unequal access to information on clinical trials. Current technologies embraced during the pandemic (e.g., QR codes, mobile passes, and RFID tags), may even offer new opportunities for sponsors and/or regulators to provide constantly accessible, current safety information to patients at their fingertips (e,g., patient information sheets from the pandemic that could be updated in real time as EUAs evolve without costly new printing/delays) - ensuring data security and privacy remains a vital element of the use of these technologies, however. While even a few years ago, such technologies were challenging and costly to implement, the pandemic has greatly accelerated the development and feasibility of implementing such patient-centric solutions. Further, we envision the potential of technology to improve access to information in a format that is patient friendly and meets the varying levels of health literacy in the broad US population. Exploring the use of technologies that can improve access to reliable information will greatly enhance trust in our health systems.

January 24, 2023

The Honorable Arati Prabhakar
Director
White House Office of Science and Technology Policy
1650 Pennsylvania Avenue
Washington, D.C. 20504

RE: Request for Information; Clinical Research Infrastructure and Emergency Clinical Trials

Dear Director Prabhakar:

The Healthcare Leadership Council (HLC) appreciates the opportunity to submit comments on the White House Office of Science and Technology Policy's (OSTP) request for information on, "Clinical Research Infrastructure and Emergency Clinical Trials."

HLC is a coalition of chief executives from all disciplines within American healthcare. It is the exclusive forum for the nation's healthcare leaders to jointly develop policies, plans, and programs to achieve their vision of a 21st century healthcare system that makes affordable high-quality care accessible to all Americans. Members of HLC – hospitals, academic health centers, health plans, pharmaceutical companies, medical device manufacturers, laboratories, biotech firms, health product distributors, post-acute care providers, home care providers, and information technology companies – advocate for measures to increase the quality and efficiency of healthcare through a patient-centered approach.

The COVID-19 pandemic highlighted the importance of private-public partnerships to respond to emergency events. Due to this unprecedented cooperation, the Food and Drug Administration (FDA) approved three COVID-19 vaccines and numerous therapeutics in record time. While we applaud the achievement of developing and approving vaccines as quickly yet safely as possible, more is needed to create a resilient framework so that clinical research can continue uninterrupted during future pandemics.

In February 2021, HLC in partnership with the Duke-Margolis Center for Health Policy published a report on how to improve our nation's disaster readiness infrastructure. The recommendations in this report focused on three different areas: improving data and evidence generation, improving care delivery approaches, and strengthening innovation and supply chain readiness. The report highlights many of the current challenges public and private entities have faced in responding to the COVID-19 health pandemic and makes recommendations on how to ease future burdens. HLC has also compiled a compendium of best practices, highlighting the efforts of our members in responding to disaster events, such as the COVID-19 pandemic as well as other large scale public health emergencies. And, in collaboration with Deloitte, HLC

prepared a compilation of private sector leader views regarding the role of the private sector in disaster preparedness and response.

We encourage OSTP to work with other federal agencies such as the Department of Health and Human Services, the Food and Drug Administration (FDA) and the National Institutes of Health (NIH) to improve interagency coordination to best identify where clinical trial infrastructure can be improved. HLC supports the work of the Accelerating COVID-19 Therapeutic Interventions and Vaccine (ACTIV) partnership as a blueprint for bringing together diverse stakeholders. Future partnerships should build upon this framework of bringing public and private groups together while streamlining regulatory approval.

Further, HLC supports efforts to strengthen the collection of real-world evidence (RWE) and reduce regulatory barriers to clinical trials while maintaining robust quality controls. This will enable private partners to quickly respond to a changing environment while limiting disruptions to clinical trials already in place. For example, decentralized clinical trials were used extensively throughout the pandemic. We encourage OSTP to examine how to continue to support these trials in a sustainable way.

HLC looks forward to working with you on improving clinical research infrastructure. Please contact Tina Grande at (202) 449-3433 or tgrande@hlc.org or Debbie Witchey at (202) 449-3435 or dwitchey@hlc.org with any questions.

Sincerely,

Mary R. Grealy
President

January 27, 2023

Office of Science and Technology Policy
Executive Office of the President
Eisenhower Executive Office Building
1650 Pennsylvania Avenue
Washington, D.C. 20504

Submitted Electronically

Re: **RFI on Clinical Research Infrastructure and Emergency Clinical Trials**

Director Prabhakar:

On behalf of IQVIA, thank you for inviting comment on your recent expansion of efforts surrounding clinical research infrastructure and emergency clinical trials. IQVIA appreciates the opportunity to offer our perspective on ways that we incentivize the discovery, development, and delivery of medical cures. IQVIA plays a significant role, both in the United States and internationally, in all phases of clinical trials to fight pandemic pathogens—from early phase clinical development through to post-approval Real World Evidence data gathering and analysis.

IQVIA is a leading global provider of research, advanced analytics and technology solutions to the life sciences industry, government agencies, academia, payers, and other healthcare stakeholders. Formed through the merger of IMS Health and Quintiles, IQVIA applies human data science — leveraging the analytic rigor and clarity of data science to the ever-expanding scope of human science — to enable organizations to reimagine and develop new approaches to clinical development, speed innovation and accelerate improvements in patient outcomes. IQVIA's services also provide proprietary information to government agencies and other healthcare stakeholders to inform decision-making.

In our response, we highlight recommendations for policy to improve pandemic readiness, aligned with the questions outlined in your Request for Information (RFI). We agree with the premise of the RFI, particularly that "the lack of a coordinated approach to clinical trials research in emergency settings has slowed the development of actionable information." We submit that it is the ability to coordinate and harness existing public and private clinical research infrastructure, scientific and technical expertise, technology, data assets and analytic power – and not the lack of infrastructure – that is key to improving pandemic response and emergency research.

Our experience across multiple epidemics and pandemics corroborates your recommendations on the need for integrating clinical research, clinical care, and disparate data sources, along with rapid establishment of collaborative public-private partnerships that enable the government to tap into the industry-leading technology, infrastructure, and expertise ahead of and throughout the next pandemic. Below are a series of suggestions based on the areas you identified in the RFI.

Governance

As the RFI accurately points out, centralized scientific and technical governance focused on enabling a coordinated response that assimilates and adjusts to an evolving evidence base is significantly needed. Based on our experience in the United States and internationally, we offer the following considerations for a centralized scientific and technical emergency research governance that can bring the insights, alignment and collaborative 'fuel' needed harness the best of what the public and private sector has to offer in service of public health.

a. Developing a governance model

During the COVID-19 pandemic, cross-agency, horizontal governance was critical for accelerating vaccines to market by providing capacity building, relationship building, and scientific expertise. As such, we believe that a future governance model should include not only heads of key federal agencies, but also a range of disciplines across the federal government, Public Health, academia, and industry (manufacturers and CROs), to provide scientific and technical advice to support decision making. The model should include a mechanism to bring in relevant domain experts from the private sector as early as possible when assessing and planning for the activation of emergency research. Having a cross-agency, horizontal coordinating body was critical to accelerating the understanding of the science and bringing vaccines to market, in great part by connecting the data silos, bringing together infection, treatment and epidemiological data (NIH, FDA and CDC). Opening the door to those who do large-scale trials (CROs) or build large scale databases as their core business is key to ensuring a rapid effective response.

b. **Ensuring right-size, right response via data analytic capabilities**

Each pandemic or emergency will present a different data and analytic need or challenge. Centralized data will not be responsive to the unique information and analysis needed to address the unique nature of each pandemic or emergency. Investment in both local public health capacity and a larger infrastructure of data, data integration and analytic capacity are needed. This data and related capabilities must be established in a flexible manner, one that allows for public-private partnerships to be built that facilitate the data flow and analytics from decentralized data sources in a timely manner.

Criteria for initiating coordinated or large-scale emerging research should be led by the science and supported by enhanced Data Surveillance capabilities and coordination. COVID-19 provided many lessons and shine the light on opportunities to expand our ability to detect, identify, model and track emerging infectious diseases. To inform each step of activation and response to emerging threats, the Federal Government, with tethers to local, state, regional and international bodies, will need to have at its ready, data analytic and integration capabilities that can assemble needed data from our nation's decentralized data sources.

There will be no one-size-fits-all approach to disease surveillance, and public-private partnerships with the agencies that primarily conduct disease surveillance, the CDC and FDA, will allow for bringing the best-in-class and state-of-the art capabilities in analytics and data integration to rapidly address the unique disease and health utilization surveillance needs of each pandemic. One function of the

governance model could be to establish working groups of private sector health data analytics and integration experts that meets regularly with the goal of ensuring both FDA and CDC have relationships, ties and visibility to best-in-class, pre-vetted health data capabilities available in the event of a pandemic.

c. **Prioritizing and rationalizing emergency research**

Selecting Priority Investigational Agents
As a complement to collective expertise of the standing membership, the committee should create, tap, and otherwise utilize available machine learning models to objectively identify and rank druggable targets and/or epitopes for vaccine research, as well as identify a list of drugs suitable for re-purposing.

Developing appropriate study designs
The governance committee should provide timely feedback on the ongoing appropriateness of novel trial designs including pragmatic trials as data matures throughout a pandemic. The governance committee should encourage research methods that are resource sparing such as platform trials. The governance committee should provide ongoing guidance on the most appropriate endpoints, data collection methods, research scales and comparators. Careful consideration should be given to the ease with which recommendations can be adopted in the backdrop of each pandemic. Consideration should be given to providing rapid approval of amendments driven by recommendations offered at the committee level.

Harmonization to committee guidance should be encouraged to allow for inter-trial comparison, where possible. Specifically, standard protocols, data collection tools and tables, listings and figures should be made available. The committee could explore the possibility of releasing protocols with simultaneous IRB approval could incentivize adoption of standards. International data sharing agreements should be coordinated with NGO and other government stakeholders to facilitate global harmonization and coordination where possible

Facilitating the use of expedited and fit-for-purpose regulatory pathways such as platform trials for vaccines against novel pathogens and consideration of alternate "real world" regulatory pathways for previously approved drugs. The committee should encourage the acceptance of pragmatic clinical trial design with real world evidence features as appropriate to the situation, research question and timing. This is particularly important for the timely evaluation of repurposed and new therapies to meet the needs of patients and clinicians during a pandemic. Such governance could also give appropriate consideration of the potential to use comparators to streamline trial enrollment and timelines.

Driving adaptation of data and reporting standards that will allow for inter-trial comparison (e.g., common endpoints and terms), including establishing **international data sharing agreements** to enable coordinated, aggregate view of safety, efficacy trends. For each disease or pathogen, there should be a minimum set of data collected for each study design. There should also be consensus on how data is collected and shared without compromising quality or privacy regardless of the location of the study. This would allow for development of

downstream forms, databases, work instructions, etc. that would save valuable time and resources. As one example, IQVIA previously developed a common data model that reduced start up time by two weeks. The governance or central committee could facilitate continuous looped feedback on preferred endpoints, scales and data collection imperatives based upon ongoing science and clinical feedback. If there is no consensus, the committee could prioritize methods for arriving at consensus

Establishing and maintaining a base between emergencies - Developing and putting operating procedures in place to rapidly detect and react to an eminent threat, including a prioritization schema for evaluating future emergency research protocols and selecting and promulgating the best study designs. Maintaining and governing site networks and driving "warm base" research.

Projecting, tracking, and monitoring trials. The Governance Committee should engage with industry – both commercial sponsors and CROs – and academia to explore what numerous existing entities could be adapted, based on the identified need. Common standards and systems would be helpful, coupled with dashboards that allow differing levels of access for various stakeholders to increase transparency. Real-Time Data Cleaning, Centralized and Risk-Based Monitoring speed up studies, and common standards could be introduced and utilized to ensure consistency across studies.

d. Developing entities for projecting and tracking enrollment and monitoring progress

Site networks, CROs and sponsors independently maintain tracking and enrollment across their respective trials. Visibility into the aggregate potential across the network can be challenging. Incentives should be provided for all stakeholders to share data with the governance committee to improve the ability to "load balance" site capacity. Data shared must be real-time and account for current, local impact of the pandemic on resources. Data should be synchronized with real-time surveillance data and appropriate demographic information for effective modeling.

Building Diversity and Equity through Institutions and Networks

The RFI pays particular attention to research networks and the need for sites. IQVIA agrees with ACRO's recommendation that the United States lean heavily on existing sites and networks during an emergency—both those funded by the NIH and the many private-sector research sites that supplement industry trials. A robust infrastructure of sites currently exists, and the United States should coordinate with and include them in capacity planning, while funding programs that address research gaps in historically underrepresented communities. Networks cobbled together during a crisis are unlikely to be successful. Before the next emergency, it is imperative that the government strengthen existing networks—whether federally funded or private—investing in new ones only when necessary.

Given its importance to the successful and timely completion of trials, the process of identifying sites for clinical trials for industry trials, including mega-trials, has become an area of specialization and expertise in the industry. The process is powered by a combination of extensive databases on experience, performance, and patient availability, sophisticated algorithms, and complementary data to forecast the right locations given site data and area competition, among many other factors. We encourage OSTP to build into its thinking ways to harness the best of what the competitive marketplace has created,

explore pre-competitive or collaborative ways to leverage these capabilities to maintain visibility to the capacity of the US research infrastructure.

Any centrally maintained intelligence will need to include a sufficiently broad range of sites to recruit potentially high-risk participants including the following: children, pregnant persons and immunocompromised populations (transplant, HIV and chronic illnesses). In addition to the ideas suggested in the RFI for improving trial diversity, IQVIA underscores the importance of upfront planning and early goal setting. Intended populations must be clearly defined at study design stage. Protocols and participant facing materials that account for community preferences are more likely to achieve diversity goals.

Use of near real-time reporting of screening and enrollment coupled with the ability to adjust recruitment strategies proved to be valuable in helping sites reach enrollment goals and ensure overall trial representativeness. Among considerations in site selection, staff reflecting local racial and ethnic diversity is likely to enhance overall clinical trial diversity. The use of historic recruitment data can help identify existing community-based research and professional research sites with proven success with diverse populations.

"Warm Base" Research for Underserved Communities

It is necessary to ensure that any research addresses meaningful clinical research questions, meets the needs of the population, and has tangible benefits for participants and the wider community. "Warm base" research can enable sites to develop expertise in clinical research and to maintain a state of readiness to respond to biological threats as they arise. It can also be used to support efforts to educate, engage and enroll citizens from underserved communities and those in areas well-served but who may feel left behind. IQVIA recommends establishing incentives for sites to complete non-vaccine work, such as access to prequalified IRBs.

Alongside data analysis to identify localized disease epidemiology, risk factors and mortality data, efforts should be made to gain the views of the local population, as well as targeting efforts to improve overall public health. Holistic statistical analysis that safely incorporates mortality information with HIPAA-compliant mortality would deepen insights of mortality trends over time.

African Americans, Native Americans, and Alaska Native Tribes have significant mortality disparity rates and often experience more severe disease earlier in life resulting in lower life expectancy. Alongside Warm Base research related to potential pandemics, target research at diseases that adversely impact these communities. Proper oversight and review by IRB and Ethics committees will be critical.
From a regulatory standpoint, accreditation of clinical trial sites meeting required standards will be necessary. Minimum site preparedness standards need to be defined, and CROs along with regulatory authorities could define criteria for site preparedness and auditing site compliance.

Emergency Master Agreement

During COVID-19, the top recommendation for sites was to use the Accelerated Clinical Trial Agreement (ACTA) "as is," which many sites and manufacturers accepted. The list of those who have agreed to use the ACTA, without negotiation, can be found on the Accelerated Research Agreement website. To

improve upon the contracting process, a focus group should be conducted to gather feedback on how to optimize the contracting process in an emergency setting. Key areas of the focus group should include the following: confidentiality, intellectual property, indemnification, compensation for injury, and IRBs. Consistent with National Institute of Health (NIH) policy and FDA recommendations, a requirement of funding should be that sites and networks agree to using a single IRB where this is warranted. During OWS, many sites implemented a waiver to use a central IRB (~95% of sites). Proactive efforts should be conducted to work with sites to identify barriers or areas of concerns to proceed with a single IRB.

International Coordination

Outbreaks need to be prevented from becoming pandemics through activities in the localities where they arise. To develop pre-pandemic preparedness and inter-governmental initiatives, governments and global NGOs need to invest further in strengthening global vaccine site networks and DCT solutions. Facilitating international alignment would provide a federal overarching governance harmonized with international pandemic preparedness. The World Health Organization, Coalition for Epidemic Preparedness Innovations (CEPI), as well as other global NGOs through co-operation with the G7 and G20 group of nations have all established positions in driving improvements for future pandemic preparedness. The federal government serves a critical leadership role in this broad approach, specifically to avoid redundancy of effort and maximum benefit of funding streams.

Further investment is needed by the global community to learn from COVID-19 and build capacity, capability, and resilience in all parts of the world. Importantly, the global community needs to ensure that Low- and Middle- income countries (LMICs) are part of the emergency response in the next pandemic situation. Much more needs to be done to build on the ongoing work in LMICs to develop clinical trial infrastructure, experience, and expertise. Below are a few additional considerations for international coordination.

Identifying International Sites. Partnering with NGOs and CROs that are engaged and active in LMIC regions will be vital as trusted partners for governments and institutions located in these countries. There is a real desire in LMICs to participate in research. The "warm base" approach must extend beyond the US to ensure we are collectively ready to drive research at the source where required.

Regulatory Considerations for International Studies. Global regulatory agencies demonstrated a significant level of agility in supporting COVID-19 clinical development in the context of a global pandemic. There needs to be further international agreement on processes for emergency clinical research so that protocols can be deployed to regions where disease is circulating rapidly. We recommend OSTP partners to develop alignment among the various international initiatives, including World Health Assembly (WHA) Resolution (75.8), CEPI 100 days mission, International Coalition of Medicines Regulatory Authorities (ICMRA), collaboration among regulatory authorities.

Global Laboratory and Medical Supply Access. An issue highlighted globally during the COVID-19 pandemic was the lack of availability of laboratory and other medical supplies due to the volume of testing taking place. We recommend adding investigators and approved research

organizations to the supply access priority list. Further, a "warm base" of laboratories needs to be considered for rapid deployment.

Tracking Clinical Research Initiatives. Several private and public databases exist to track and make available key pieces of clinical trial information, including WHO's International Clinical Trials Registry Platform (ICTRP) and websites such clinicaltrials.gov. While databases can support the pooling of information, this needs to be mined with appropriate analytics to create live dashboards to support visualization of vast, chronological data sets, highlight diversity of sample, research into variants etc., on a regional and global scale. Additionally, such platforms should be used to connect trial teams, prevent duplication of efforts, and understand differences in data.

On behalf of IQVIA, thank you again for the opportunity to share our comments and recommendations for the next phase of discussion about clinical trials infrastructure. If you have any questions about the recommendations provided, please do not hesitate to contact me at andrew.barnhill@iqvia.com or 910-620-7622. I will be happy to connect you with any of our subject matter experts from who work tirelessly to advance clinical research. We look forward to participating further in this important conversation about the federal government's role in responding to emergencies with well executed clinical trials.

Regards,

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January 27, 2023

Submitted via email to the White House Office of Science and Technology Policy: emergencyclinicaltrials@ostp.eop.gov

Re: OSTP Emergency Clinical Trials RFI

The Association of American Medical Colleges (AAMC) appreciates the opportunity to respond to the Office of Science and Technology Policy (OSTP) Request for Information: Clinical Research Infrastructure and Emergency Clinical Trials (87 Fed. Reg. 64821).

The AAMC is a nonprofit association dedicated to improving the health of people everywhere through medical education, health care, medical research, and community collaborations. Its members comprise all 156 accredited U.S. medical schools; 14 accredited Canadian medical schools; approximately 400 teaching hospitals and health systems, including Department of Veterans Affairs medical centers; and nearly 80 academic societies. Through these institutions and organizations, the AAMC leads and serves America's medical schools and teaching hospitals and the millions of individuals across academic medicine, including more than 191,000 full-time faculty members, 95,000 medical students, 149,000 resident physicians, and 60,000 graduate students and postdoctoral researchers in the biomedical sciences. Following a 2022 merger, the Alliance of Academic Health Centers and the Alliance of Academic Health Centers International broadened the AAMC's U.S. membership and expanded its reach to international academic health centers. Learn more at aamc.org.

From the onset of the COVID-19 pandemic, the AAMC's member medical schools and teaching hospitals were at the front lines of the response, treating patients, developing diagnostics, studying and administering therapeutics and working to address the needs of underserved communities. We agree with OSTP's assertion that the inability to fully and rapidly coordinate efforts on a national scale hampered the COVID-19 pandemic response on many fronts, including the lack of aggregated clinical data that could have sped our understanding of the infectious disease's transmission, assessment of whether certain treatments were effective, and development of diagnostics and therapeutics. In particular, the opportunity to study and understand the virus' impact through large-scale clinical trials was lost with the initiation of many local research protocols that often were poorly designed or insufficiently powered to provide meaningful actionable information. These inadequate trials represented a lost opportunity, and also raised ethical concerns by enrolling human subjects in trials that could

never have yielded meaningful, generalizable results. In addition, the exclusion of communities and populations that have been historically marginalized and who are generally underrepresented in clinical research served to increase the disparate impact of COVID-19 on these communities. For all these reasons, we welcome the current efforts by OSTP to develop new models or strengthen existing networks to organize coordinated clinical trials in advance of a "nationally or internationally significant biological incident."

Here we offer general comments on the RFI and the types of inquiries that we recommend be the focus of the next conversations in an ongoing effort and each of the four broad topics addressed by the RFI.

General Comments

The ambitious scope of this project, as OSTP has explicitly recognized, presents challenges to successful implementation. As OSTP and federal agencies begin to move forward, the AAMC urges OSTP to continue a transparent, multisector approach. This strategy should be aided by existing scholarship and previous efforts to find consensus on clinical trial agreement terms, as previous efforts have been hampered by impasses. There should be meaningful, bidirectional engagement with the communities the effort seeks to involve as active participants. The activities should reflect the lessons learned and documented regarding the successes and challenges of research on COVID-19. Finally, the efforts should leverage existing networks of connected institutions and researchers and engage them in stepwise actions through pilot studies to assess the feasibility and effectiveness of a larger effort prior to its implementation.

The listening sessions OSTP held to discuss this RFI were both promising examples of transparency in the development of OSTP's thinking and clear reminders of the extraordinary breadth of opinions, concerns, and considerations this effort raises. Although a range of national and international experts provided worthwhile perspectives and cautions in those sessions, we urge OSTP to include additional voices who could provide much needed direct community feedback early in this process. As has been demonstrated countless times in the context of clinical research, efforts to incorporate community voices in a way that demonstrates trustworthiness must commence at the beginning of the project and facilitate genuine partnership throughout.[1]

To this end, and as referenced below, the AAMC suggests the formation of one or more multi-sector groups tasked with taking a systematic approach to proposing the governance structure for this effort and criteria for the activation of clinical trials through the resulting network. This effort requires the voluntary and active participation of many organizations, including those that have not previously participated in federally-overseen clinical trials. The answers to the

[1] See, e.g., the AAMC Center for Health Justice's co-developed *Principles of Trustworthiness*, available at: https://www.aamc.org/trustworthiness.

important questions posed in the RFI require not only the input of experts, but also engagement and buy-in from across the biomedical research community. Early and broad engagement to arrive at consensus, rather than a "top down" approach from a panel of federal representatives alone will accomplish these two goals in parallel.

Additionally, we note that when the RFI was issued there was some concern in the biomedical research community about describing this work as "emergency clinical trials." It is worth considering that "emergency research" is well understood to describe a relatively uncommon situation when, for a particular protocol or individual, pre-planned research reviewed by an institutional review board can move forward in the absence of informed consent.[2] We suggest that an alternative term such as "coordinated clinical trial readiness" be used instead to avoid suggesting to the public that clinical research during a pandemic or other related incident would be undertaken in all or most cases without the need for informed consent.

Governance for Emergency Clinical Trials Response

The governance and primary coordinating structure, including robust cross-agency management and engagement, will be an essential component of a coordinated clinical trial response. We note at the outset that in the face of a pandemic, this coordination would have to be fully integrated into the national pandemic response. All stakeholders in this clinical trial response would benefit from reassurance that the data elements for protocols being developed would be aligned with any data being requested of hospitals and health departments to capture information about the spread and impact of the threat. To the extent possible, the clinical trial's data requirements should match those required for public health purposes. Because the same organizations that would be asked to implement these clinical trial protocols will also be addressing the pressing health needs of the impacted communities, all actions taken to facilitate an effective scientific and clinical response to the biological threat must be working toward a common goal. Similarly, consideration of required data formats and repository access should be undertaken in collaboration with the Centers for Disease Control and Prevention (CDC) and other federal agencies well before an emergency to facilitate streamlined and consistent data transfer to address both public health and clinical research needs. As with many aspects of this initiative, the thorny issues of electronic system interoperability and privacy will need to be addressed.

The AAMC notes that in the section of the RFI on "governance," the set of questions and proposed responsibilities seem to address two disparate sets of activities: 1) those required to develop the procedures and technical specifications to set up the initiative and 2) the decision-making and oversight activities that would take place during a pandemic or other public health emergency. The AAMC recommends that a federal entity should serve in a coordinating role for

[2] See FDA Guidance, *Exception from Informed Consent Requirements for Emergency Research*, available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/exception-informed-consent-requirements-emergency-research.

the first set of activities and retain primary responsibility for the second set of activities, engaging the multisector partners described below as advisors.

This section of the RFI asks for specific criteria or responses to issues that are essential for the successful implementation of a national effort. While we agree that each must be addressed, we suggest that they be answered through the establishment of multisector working groups with the specific charge to propose such criteria and present a consensus viewpoint for more efficient responses from the broad community. We recommend that OSTP look to the Department of Health and Human Services' Office of the Assistant Secretary for Health's Federal Plan for Equitable Long-Term Recovery and Resilience for a model on how to coordinate both federal resources and the local organizations and assets that represent all the vital conditions communities need to thrive and that would be useful in ensuring that this effort is maximally successful.[3] In addition to the relevant federal agencies, including the National Institutes of Health (NIH), Department of Health and Human Services Office of Human Research Protections (OHRP), Food and Drug Administration (FDA) and CDC, the groups should include participants from across all sectors that will be expected or invited to participate in this initiative. The institution-specific and sector-specific responses to this RFI, along with the input provided directly to OSTP through listening sessions, could serve as a starting point for these groups, rather than for a final set of criteria issued by OSTP.

Once a widely supported governance and decision-making structure has been created, the process for developing the clinical trial protocols will be, in our estimation, the most important factor in the success of the initiative as whole. This process must provide all partners, from established research institutions to federal agencies to community clinics to the general public, the opportunity to understand, well in advance of a public health emergency, how those protocols will be created. Any institution that considers entering into an Emergency Master Agreement will need to have the confidence that the clinical trial protocol or protocols developed and activated under the agreement have scientific validity, the ability to answer the most important clinical questions, feasibility, generalizability, a mechanism to address protocol revisions based on new information, considerations for international collaborators or subjects, and a way to address institution-specific concerns. We suggest that the framework for this process be prioritized for development, as this would likely be an element that would take time to build broad community consensus.

One approach a governance group could consider is whether, instead of or in addition to a single clinical trial protocol implemented across all participating sites, a national effort could rapidly identify the most essential key data elements and endpoints that any clinical trial protocol should collect to be part of a national data collection effort. A scientific protocol working group could

[3] See the framework and resources at: https://health.gov/our-work/national-health-initiatives/equitable-long-term-recovery-and-resilience.

set criteria that a clinical trial would need to meet to be eligible to contribute to the data repository (e.g., inclusion criteria, whether an investigational agent was being studied), and then develop the specific fields, metadata, and format that would be required. By making these data requirements publicly available, it might broaden the reach of this effort to organizations that had not previously entered into the Emergency Master Agreement or that had elected not to solely implement the distributed protocol.

Identifying and Incentivizing Research Institutions and Networks

The RFI correctly identifies the key barriers to the monumental shift from a decentralized clinical trial approach with some collaboration across networks of institutions to the development and implementation of a single clinical trial protocol implemented simultaneously across many types of organizations. Although there is wide recognition of the need to improve clinical trial infrastructure as a whole, especially in the context of a biological threat, it will be a challenge to incentivize the voluntary participation of a host of organizations with vastly different levels of research experience, number of research staff, existing clinical trial infrastructure, and motivation to take on new research activities in the face of a threat on the scale of COVID-19.

The first steps in building the network of sites that could participate in such an effort should be to identify the existing networks and connections that could be readily activated. Not only can these networks and consortia extend the number of potential research sites, they can also provide OSTP with considerable information about the advantages and challenges with implementing a single protocol or process across a set of organizations with already-established connections. As one key example, the Clinical and Translational Science Awards (CTSA) program administered by the National Center for Advancing Translational Sciences (NCATS) was developed to address precisely the kinds of challenges and inefficiencies in translational research that OSTP seeks to address with this current effort. Engaging with both NCATS and CTSA institutions would be instrumental in assessing the utility of using this network or working to create new models for connecting institutions.

As further discussed below in the context of building clinical trial infrastructure through "warm base" research, a more complete model will need to include information about how this research and the contemplated infrastructure would be funded. Incentives for joining this network through a master agreement will need to go beyond the ability to participate in a novel mechanism for gathering data in a pandemic to a more sustainable engagement in the clinical research ecosystem as a whole.

The AAMC applauds OSTP for considering as a priority the inclusion of organizations that serve underrepresented populations and can engage underserved geographic and demographic communities. As OSTP is exploring ways to increase this participation, leveraging the

connections between academic institutions and their community and public health partners could open additional avenues of communication and sources for working group participants.

"Warm Base" Research

As described in the RFI, a core component of an accelerated clinical trial response to an infectious disease outbreak or other public health emergency is the rapid distribution of one or a small number of key protocols for many sites to implement simultaneously. In order to maximize the reach of these trials to all impacted geographic areas and underserved areas, the RFI raises the possibility of supporting or facilitating so-called "warm base" research. This is described as a mechanism through which staff at a site unexperienced with some or many aspects of conducting clinical trials gain familiarity with the regulations, procedures, and data collection methods of clinical trials in advance of the need to activate a specific protocol in the context of a public health emergency.

At its core, what this describes is the concept of research capacity building, a sorely needed and resource intensive endeavor. The AAMC is supportive of efforts that build clinical trial capacity and urges OSTP to consider how these efforts might be initiated and funded at sites that currently have little or no capacity to conduct clinical research. We caution too that even simple data collection trials created to build this capacity through "warm base" research must themselves be ethically and scientifically sound, and conducted and overseen by trained research staff. Such training and capacity building efforts are welcome but might constitute a heavy lift for a federal initiative that is simultaneously developing the governance and process for the initiation of a coordinated clinical trial initiative. As with many aspects of this effort, testing the feasibility of supporting the research through pilot studies will be most beneficial.

Emergency Master Agreement

A core structural component of the effort being discussed is the so-called "Emergency Master Agreement," which would seek to settle core contract terms well in advance of a biological threat. A laudable goal, we note similar efforts over decades to settle on key terms in clinical trial agreements have had limited success. Beginning the process with a comprehensive look at the impact of these harmonization efforts would be of use to OSTP. In many cases provisions such as indemnification and subject injury have been difficult to resolve even in more successful templates.

The effort seeks to engage many types of organizations beyond academic medical centers to carry out one or more protocols. The necessary terms, provisions, and capacity assessments may vary by type of organization and type of trial. Observational studies, medical record reviews, and interventional trials with known or investigational agents will each require very different infrastructure and expertise. It may be necessary to create a tiered set of agreement provisions,

allowing each institution to opt in to a threshold set of terms based on its current capacity for conducting clinical trials.

A question that will need to be addressed is how the nationally developed protocols will be coordinated with (or in some cases prevent) other clinical trials developed simultaneously by industry, academic health centers, or other organizations that have signed the Emergency Master Agreement. A threshold issue for many institutions will be whether, by signing the agreement, that institution would be contractually prohibited from initiating or participating in other clinical trials. Without knowing in advance what the agreed-upon trials would seek to answer, this might have a chilling effect on the willingness of some organizations to participate.

The AAMC and its member institutions stand ready to assist the OSTP and federal agencies in considering how greater coordination and the building of clinical trial infrastructure could help us better respond to the threat posed by another infectious disease outbreak or public health emergency. Please feel free to contact me or my colleague Heather Pierce, Senior Director for Science Policy and Regulatory Counsel (hpierce@aamc.org) about these comments or other ways in which we can help.

Sincerely,

Ross McKinney, MD
Chief Scientific Officer

cc: David J. Skorton, MD, President and Chief Executive Officer

MITRE's Response to the OSTP RFI on Clinical Research Infrastructure and Emergency Clinical Trials

January 26, 2023

For additional information about this response, please contact:

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About MITRE

MITRE is a not-for-profit company that works in the public interest to tackle difficult problems that challenge the safety, stability, security, and well-being of our nation. We operate multiple federally funded research and development centers (FFRDCs), participate in public-private partnerships across national security and civilian agency missions, and maintain an independent technology research program in areas such as artificial intelligence, intuitive data science, quantum information science, health informatics, policy and economic expertise, trustworthy autonomy, cyber threat sharing, and cyber resilience. MITRE's 10,000-plus employees work in the public interest to solve problems for a safer world, with scientific integrity being fundamental to our existence. We are prohibited from lobbying, do not develop or sell products, have no owners or shareholders, and do not compete with industry. Our multidisciplinary teams (including engineers, scientists, data analysts, organizational change specialists, policy professionals, and more) are thus free to dig into problems from all angles, with no political or commercial pressures to influence our decision-making, technical findings, or policy recommendations.

MITRE has multiple experiences relevant to the clinical trials infrastructure objectives stated in the RFI, such as those listed below:

- Established and co-leads the Coalition for Advancing Clinical Trials at the Point of Care (ACT@POC), which brings together health systems, community-based care organizations, health research organizations, and other collaborators to build an adaptable and responsive clinical trials network focused on increasing participation, improving patient access, and facilitating development of targeted therapies with important impact on patient outcomes.[1]
- Established and co-chaired the COVID-19 Healthcare Coalition (C19HCC), a private-sector led response that brought together healthcare organizations, technology firms, nonprofits, academia, and startups to preserve the healthcare delivery system and help protect U.S. populations.[2] The Coalition built rapid clinical studies based on common data models and collection techniques. Through these efforts, the coalition was able to answer key clinical questions quickly and effectively on the use of targeted therapeutics in the early days of the pandemic.
- Explored and demonstrated results for use cases under CodeX.[3]
    - The *Integrated Trial Matching for Cancer Patients and Providers* use case is exploring how to make cancer clinical trial screening more equitable and easier for all patients and providers.[4]

[1] Advancing Clinical Trials at the Point of Care. 2023. MITRE, https://actpoc.org/. Last accessed January 18, 2023

[2] COVID-19 Healthcare Coalition. 2022. MITRE, https://c19hcc.org/#. Last accessed January 18, 2023.

[3] CodeX Home. 2023. CodeX, https://confluence.hl7.org/display/COD/CodeX+Home. Last accessed January 18, 2023.

[4] Integrated Trial Matching for Cancer Patients and Providers. 2022. CodeX, https://confluence.hl7.org/display/COD/Integrated+Trial+Matching+for+Cancer+Patients+and+Providers. Last accessed January 18, 2023.

- The *Integrating Clinical Trials and Real-World Endpoints* use case is demonstrating that electronic healthcare records (EHRs) can provide high-quality clinical trial data in a way that is both more efficient and less burdensome than the current system of using separate and expensive curation processes.[5]

Introduction and Overarching Recommendations

MITRE's recommendation for emergency clinical trials is a system for routine clinical trials that is regularly exercised, routinely improved upon, and available for emergency use when needed. Such a network would ideally have several features, which we discuss in our response to the adjacent "data" RFI.

Implementing such an approach will be complicated as the healthcare system is fragmented, and the policies, governance, oversight, and leadership are siloed across multiple federal agencies, resulting in challenges in rapid, efficient, evidence-based implementation of emerging research and preparedness for emergency clinical trials. Interagency collaboration is necessary to accomplish the collaborative networks and infrastructure investments to safeguard our healthcare system for the future. Our observations and responses focus on the following key themes:

1) Collaboration and coordination across multiple public agencies and private entities is needed to create a holistic strategy to map efforts so that duplications and gaps can be identified and addressed.
2) Community representation and participation in co-designing the emergency clinical trial research infrastructure, pilots and practice runs is essential to simplify and streamline data pipelines and requirements and foster trust with vulnerable and under-resourced communities.
3) Warm base research network that offers centralized and federated models that can be utilized for clinical research and extensible to pandemic/emergency response.

Responses to Questions Posed in the RFI

1. Governance for emergency clinical trials response

a. Descriptions of models that could be used to establish a U.S.-level governance structure for emergency clinical trials.

The first step in determining an effective governance structure for this activity is to recognize that it will predominantly be a voluntary collaboration spanning a wide range of entities, each with varying levels of commitment and resources. Participants must not only feel sufficient value to warrant their continued participation but also that they have some input or influence over decisions made. That said, there must also be a strong leadership and coordination function to succeed.

[5] EHR Endpoints for Cancer Clinical Trials. 2022. CodeX, https://confluence.hl7.org/display/COD/Integrated+Trial+Matching+for+Cancer+Patients+and+Providers. Last accessed January 18, 2023.

MITRE and the Office of Management and Budget (OMB) previously encountered such a juxtaposition when designing the operating model of OMB's proposed *Government Effectiveness Advanced Research* Center. After reviewing multiple options, we settled on an approach that would also be effective in this context. This design had three components:

- A **federal government role** to leverage resources, data, and the varied opportunities for piloting ideas that are distributed throughout the government.
- A **private sector network of networks** to bring together and leverage private sector expertise and resources from throughout industry, academia, research organizations, and non-profits (and in this case, various healthcare-specific entities).
- An **"operator" entity** to serve as both a strategic and tactical coordinator and as a trusted third party between the government and private sectors.

Federal Government

Even though the federal government would not be individually deciding and directing activities in this model, it still has critical leadership and support roles as the preeminent catalyst of the activity. It also has unique qualities that it can bring to bear across the collection of the group's activities:

- Most influential determiner of national priorities
- Power to declare public health emergencies (and to help focus activities during those emergencies)
- Nation's largest sponsor of research
- Holder of enormous amounts of data on a variety of matters
- Unprecedented ability to convene executives from various communities together
- Breadth of piloting environments and opportunities
- Largest and widest audience for publicizing the group's activities and its impact

Federal government activities would need to be coordinated by a White House-led interagency body that leverages proven science and technology (S&T) management concepts and approaches highlighted in the MITRE document *Interagency S&T Leadership*.[6]

Private Sector

Our analyses showed that success would depend on reaching large groups of thought leaders from throughout the extended private sector ecosystem quickly, systematically, and strategically. Rather than taking a shotgun approach of targeting entities directly, the plan instead would be to identify *existing* networks (with diversity of thought, experiences, and geographic locations) to leverage and pull their members into the broader collaboration. We also recognized that each participant's role would vary by their level of commitment and involvement and would generally fall into one of three categories:

[6] D. Blackburn. Interagency S&T Leadership. 2016. MITRE, https://www.mitre.org/sites/default/files/publications/pr-16-0916-interagency-s-and-t-leadership.pdf.

- **Knowledge** – Provide subject-matter experts to aide in strategic planning and to lead or participate in collaborative (involves the most participants).
- **Resources** – Capital investments and assets such as facilities, data, tools, and human capital to facilitate execution.
- **Governance** –These entities would help shape the strategic direction of the collaboration and its supporting activities (involves the least participants).

An important note is that each private sector network and individual participant will need to feel there is sufficient value recovered from their investment(s) in the initiative's activities. This will vary by the category of their involvement and their individual areas of focus in their normal business.

We have seen aspects of this design and related considerations on smaller scales in a variety of contexts, including clinical trials. In the COVID-19 Healthcare Coalition, for example, we learned that given the current difficulties in sharing health data, the ideal model requires options for both centralized and federated capabilities.

MITRE also acted, in the Department of Health and Human Services Office of the Assistant Secretary for Preparedness and Response's (ASPR) COVID-19 Real World Evidence for Monoclonal Antibodies (mAbs) Project, as a trusted third-party data aggregator and analytics team. In collaboration with academic medical centers and care delivery systems, we worked to (1) gather and analyze real-world data to develop real-world evidence (reflected in predictive models) regarding the safety and effectiveness of mAb treatments for COVID-19, including risk stratifications to help prioritize the use of mAbs and (2) identify effective and improved care models, including recommendations for the removal of barriers to accessing and using mAb treatments.

In Europe, several federated learning networks have been built using the DataShield open-source capability.[7] Such networks might decrease the risk for organizations wishing to participate, potentially in low health IT resourced organizations serving diverse and disadvantaged populations. MITRE demonstrated federated learning capabilities during C19HCC famotidine, remdesevir, and convalescent plasma studies and more recently, has developed an internal prototype demonstrating the use of a DataShield network for pandemic response queries using synthetic patient records. MITRE has also been in discussion with commercial vendors to assess the feasibility of similar federated capabilities in the U.S.

Operator

In addition to serving as the trusted third party between the government and private sector, driving them to consensus decisions, the operator entity would also oversee the management and operations of the selected activities. The operator would require a staff (or connected associates) with skills in areas such as program management, communications, strategic partnering, market research, medical technology and business strategy, policy and public administration, legal, finance, contracts, and legislative affairs. The operator would focus on activities such as those listed below:

[7] A. Gaye, et al. DataSHIELD: taking the analysis to the data, not the data to the analysis. 2014. International Journal of Epidemiology, https://doi.org/10.1093/ije/dyu188. Last accessed January 24, 2023.

- Facilitation – Serve as a liaison and formal interface between the White House, federal agencies, and private sector networks.
- Network Management – Build and maintain the partner networks, establishing and nurturing the formal and informal relationships needed to execute the initiative's plans.
- Market Research or Scanning – Engage the network organizations to scan their members to identify trends, issues, and solutions that may impact or influence research initiatives or provide insight into new avenues of investigation.
- Research Agenda – Facilitate and manage the process of assembling and refining the initiative's Research Agenda, combining priorities from the National Science and Technology Council and private sector participants with any relevant trends, issues, or promising approaches learned from market scanning.
- Events and Publications – Design, organize and manage events, programming, and publications that deliver education and information to agencies, network partners, and research teams.
- Research – Engage network partners, spur interest in contributing to research initiatives, and execute research addressing collaboratively identified priorities.
- Data Management – Collect, maintain, and enable sharing (when allowed and appropriate) of data amongst participants. Serve as a trusted third party for sensitive data.
- Demonstration Pilots and Proofs of Concept – Facilitate access to data, research infrastructures, and opportunities within agencies to pilot, conduct proof of concept and demonstrations around research initiatives and potential solutions.
- Reporting – Monitor progress on research initiatives and evaluate and report on outcomes achieved.
- Feedback – Distill insights derived from research and share with agencies and private sector partners to inform future strategy and research priorities; provide input to OSTP and OMB to help strategically plan future strategies and budget requests.
- Communications – Develop a comprehensive communications program that will promote the work and capabilities of the initiative and individual partners, increasing awareness of research initiatives, outcomes, and recommendations.

e. Mechanisms for tracking institutions, networks and sites that might be able to participate in emergency research, to ensure adequate potential for enrollment and adequate geographic coverage, domestically and internationally.
   i. Criteria for establishing a target number and location of sites needed to support clinical trials in case of emergency.

MITRE's recommended approach envisions predominantly focusing on identifying and leveraging existing diverse networks rather than separately tracking and targeting institutions individually. Doing so not only enables economies of scale but also helps ensure these existing activities view the initiative favorably rather than as a threat. The operator entity would be tasked with managing relationships with these networks, which would include collaborating with

leadership to petition their membership for information as well as to gather and organize the returned information for analysis and future tracking.

The target number and location of sites needed to support research should be determined during trial design by experienced evaluators, based on scientific criteria such as sample size and power needed to detect a difference, significance, number of patients and sites/regions impacted, probability and risk of outcomes and end points of interest, and anticipated effect size.

f. Procedures whereby the U.S. Government, together with external stakeholders, could oversee the development of clinical trial protocols and, where appropriate, the selection of investigational agents. It would be particularly helpful to get input on whether there is a role for public-private partnerships in this context.

In MITRE's recommended model, this would be a task assigned to the operator entity, who would perform the task by joint analysis and obtaining consensus from government and private sector partners. Existing public-private partnerships would be leveraged as part of this planning process.

g. Best practices, including "quality by design" principles, for designing trials so that they capture the data needed without unnecessary complexity that can complicate execution.

MITRE recommends that the data needed to support emergency clinical trial research should be piloted, prototyped, and moved into the relevant policy and regulatory constructs prior to need. The data should be conformant to a common data model to facilitate the development of study designs and protocols that can be universally implemented. Such data should derive from routine care provision and be used for the monitoring of routine care as frequent use will ensure that the data is available for emergency purposes when needed. MITRE provides additional details in its response to the related "data" RFI.

Quality by design principles informed critical research during the COVID-19 pandemic, such as the RECOVERY trial, are relevant to the conduct of point-of-care trials. The ASPR mAbs study was designed to use existing real-world data collected from the patient's electronic health record, which was then supplemented with additional study data. Regardless of study design, the protocol must specify a common data model and common study endpoints that can be scaled to facilitate more rapid, robust, and valid evidence generation.

2. Identifying and Incentivizing Research Institutions and Networks; Building Diversity and Equity

b. Effective ways to increase diversity among study participants and investigators, and to expand clinical research sites into underserved areas.

One of the most valuable ways of increasing clinical trial diversity is by simplifying trials and reducing their costs.

Data collection is one factor that limits clinical trial diversity. A typical trial includes numerous site visits and vast amounts of data collection (dozens of pages per patient). Those pages of data

collection are burdensome for both trial sites and patients and limit where trials can be conducted as few community sites have the time or resources to collect that much data.

In many cases, simpler trial designs and a quality-by-design approach can reduce the need for data collection. Experts agree that many trials are too complex, and that simpler, streamlined trials would allow us to answer many important clinical questions. This, in turn, will enable us to reach more diverse patients who do not have the time and resources to participate in trials at large academic medical centers.

Another way to reduce data collection burden is to leverage technology. For example, technology can help us embed data collection within the EHR to make data collection less burdensome for clinicians, augment data collected in clinical trials with real-world data obtained from electronic health records and collect data directly from patients. MITRE discusses this in more depth in the accompanying "data" RFI response.

As we make efforts to increase the diversity of clinical trials, we should explicitly benchmark, monitor, and seek to reduce per-patient costs. Clinical trial costs have reached over $40,000 per patient on average; this represents a level of spending and resources that will be difficult to sustain over the course of a pandemic.[8] MITRE has spoken with experts and leaders in clinical trial execution, and there is broad agreement that by simplifying trials and leveraging new tools and technologies we must reduce clinical trial costs in the United States by a factor of ten. If we can make trials less costly, we will have an easier time building, executing, and expanding broad clinical trials that reach beyond the patient population of highly resourced academic medical centers.

3. "Warm Base" Research

Our healthcare system does not have sufficient experience or expertise in conducting point-of-care trials. A robust "warm base" of point-of-care research can help the United States be better-prepared to meet the challenge of a pandemic. Warm base research supports a better clinical trial workforce, better tools for conducting point-of-care trials, more efficient and streamlined processes and technologies, and a broader more inclusive network of clinical trial sites.

Warm base research should address critical public health needs and better outcomes for patients. MITRE recommends that the government identify and support research in critical disease areas and address specific research questions in which point-of-care research can add value. We recommend focusing on research areas that address the following concerns or criteria:

- address disease areas in which there is high health burden and unmet medical need, particularly in vulnerable and underserved communities
- Areas for which there are specific research questions that, if answered, could lead to meaningful benefits to those communities
- Little commercial incentive to carry out the research (i.e., the private sector is unlikely to fund the necessary research)
- Questions that point-of-care approach can be used to answer

[8] T. Moore, et al. Variation in the estimated costs of pivotal clinical benefit trials supporting the US approval of new therapeutic agents, 2015-2017: a cross-sectional study. 2020. BMJ Open, https://bmjopen.bmj.com/content/10/6/e038863. Last accessed January 24, 2023.

Site Considerations. To conduct clinical research, sites must have the tools, technology, and expertise to collect and analyze data for clinical research and share that data using common data standards such as Observational Medical Outcomes Partnership (OMOP) or Fast Healthcare Interoperability Resources (FHIR). While many academic medical centers possess these resources, community sites that are unaccustomed to conducting clinical research may need additional training and support. This support can come in several forms: (1) a warm base research network may wish to provide sites with easy-to-use, accessible, and affordable tools to support embedded data collection and data exchange and (2) training and support for the use of these tools. In certain cases, a centralized study coordinating center can perform certain functions on behalf of research sites, such as remote monitoring and data analysis.

To ensure that research sites can participate in a network and contribute reliable data in a clinical trial, we recommend developing and conducting technology "readiness assessments." These assessments would include "connectathons," simulated data collection and exchange, or other structured interactions with trial sites that would validate sites' ability to collect study data using their electronic health records systems and exchange that data reliably. More broadly, we recommend that a warm-base point-of-care trial network include comprehensive support for new sites that are unaccustomed to conducting clinical research. This support should come in the form of technology assistance, training, workforce development, and financial incentives.

Beyond point-of-care. While point-of-care trials in community settings can answer some research questions, they are not as effective at evaluating investigational therapies. Yet some of the principles of point-of-care trials can be carried into other research areas. More broadly, we recommend building any warm-base network around the concept of embedded platform trials: technology-enabled clinical trials embedded into clinical practice that leverage real-world data, including data collected in electronic health records and from patients own devices, and use AI and machine learning to improve trial design, recruitment, and execution.[9,10,11] These platforms can be readily adapted to conduct research in a pandemic.

REMAP-CAP is one example of such a trial which was readily repurposed into a COVID trial during the pandemic. Within the context of a platform trial, a study can be stood up quickly, and at lower cost than traditional "one-off" trials.[12,13]

[9] D.Greenbaum. Making Compassionate Use More Useful: Using Real-World Data, Real-World Evidence and Digital Twins to Supplement or Supplant Randomized Controlled Trials. Pacific Symposium on Biocomputing, https://psb.stanford.edu/psb-online/proceedings/psb21/greenbaum.pdf.

[10] O. Inan et al. Digitizing Clinical Trials. 2020. Digital Medicine, https://doi.org/10.1038/s41746-020-0302-y. Last accessed January 23, 2023.

[11] S. Kolluri, et al. Machine Learning and Artificial Intelligence in Pharmaceutical Research and Development: A Review. 2022. the AAPS Journal, https://doi.org/10.1208/s12248-021-00644-3. Last accessed January 23, 2023.

[12] REMAP-CAP Response to the COVID-19 Pandemic. 2022. REMAP-CAP, https://www.remapcap.org/coronavirus. Last accessed January 23, 2023.

[13] M. Neal, et al. Emerging clinical trial designs may accelerate translation in hematology: lessons from COVID-19. 2022. Blood advances, https://ashpublications.org/bloodadvances/article/6/16/4710/485709/Emerging-clinical-trial-designs-may-accelerate. Last accessed January 23, 2023.

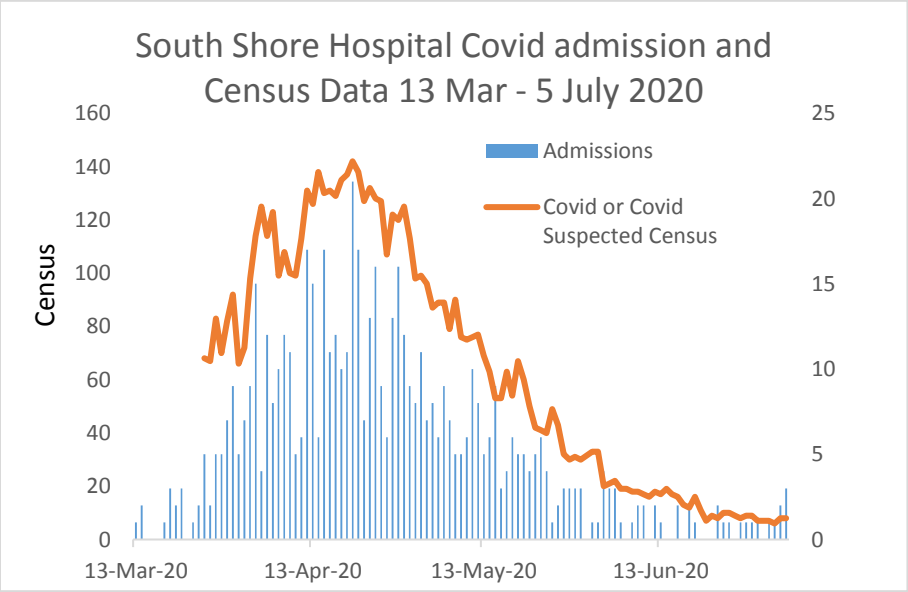
To: Dr. Carrie Wolinetz
OSTP Deputy Director for Health and Life Science

Grail Sipes
Assistant Director for Biomedical Regulatory Policy

RE: Emergency Clinical Trials RFI

Thank you for your interest in expanding patient access to experimental therapies during pandemics or other unanticipated surge conditions. The South Shore Hospital (SSH) is in Weymouth Massachusetts. It has 387 licensed beds, of which 290 are Medical Surgical Beds. We have a mixed service ICU with 22 beds. Our hospital sees approximately 120,000 Emergency Department visits per year, making us among the busiest in the state. SSH owns its own prehospital service, with EMT/Paramedic. At the time of the first COVID-19 pandemic surge, we were the primary 911 EMS service for the town of Weymouth, and a backup for most other towns in our catchment area. Our SSH EMS has offered Mobile Integrated Health (MIH) services since 2019. Our primary service area includes 800,000 – 1 Million patients who reside between Boston, Massachusetts and the Cape Cod Canal. Our research enterprise in March of 2020 was composed of a Director of Research, the Institutional Review Board (IRB) Chair, and a clinical research coordinator.

Between 13 March 2021 and 1 January 2023, we admitted 5,197 COVID-19 patients to our hospital, 598 of these admissions came in the first surge, 13 Mar through 5 July, 2020. Of these patients, 178 died. Our peak census was 141 patients. We were able to double our ICU capacity, with a peak ICU census of 36 vented patients. Our mortality rate in Surge 1 was approximately 25% overall and 50% for patients requiring intubation. We have had three subsequent surges, to date treating over 5,500 patients. Among these patients we have had 520 deaths.



In March of 2020, anticipating a pandemic crisis, SSH IRB leadership instituted the following:

1. The IRB was put on 24 hour notice for ad-hoc meetings. Members were enthusiastic about "doing what they could" during the crisis.
2. The Director of Research established connections with a wide variety of potential pharmaceutical sponsors and screened and shared industry proposals within 24 hours of receipt.
3. We informed our Academic Partner Hospitals in Boston that we were ready and able to contribute to clinical trials they might wish to propose.
4. The Director of Research and the IRB Chair recruited primary investigators from our medical staff and aided in the preparation of IRB submissions and trainings.
5. The Director of Research worked with each of the components of the institution's Human Research Protection Program to ensure all required and regulatory reviews and functions were completed in a timely manner.
6. The Human Research Protection Program became an active member in the institution's emergency preparedness plan and committee.
7. Our research program prioritized studies proposing to bring novel therapies to the bedside above other work.
8. We used hospital sponsored secure texting to streamline compassionate use applications, overseen by the IRB Chair and the Department of Research.

Using this structure we screened and evaluated a number of Phase 1, 2, 3, expanded access, IND exempt and device clinical trial protocols. The IRB ultimately approved 7 COVID-19 clinical trials. Our most effective clinical trial was initiated 10 days after receipt of the protocol from the sponsor, following two reviews by the IRB, and several administrative and ancillary reviews. All told, we enrolled 33 inpatients, 5.5% of all COVID-19 patients, in clinical trials in Surge 1. Using our MIH service, we were also a leading center in a trial of home delivered Remdesivir, enrolling 15 patients in a clinical trial of home infusion of this agent.

Building on our experience delivering Remdesivir in patient's homes, through 31 December 2022 our MIH team has treated 802 COVID-19 patients in the community. Many received Remdesivir, some were given Monoclonal antibody treatment, avoiding hospital admission. This is an example of clinical research being put to immediate general use in a time of crisis.

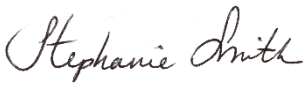
Of several collaborative sponsored studies proposed by our AMC partners, only one was able to start at SSH. A second trial was rendered moot by negative data from other studies before it could be approved in Boston. Our success bringing novel therapies to the bedside came from working with industry. AMCs were simply unable to produce the necessary protocols and approvals before the first surge was finished.

With the focus on delivering potentially life-saving or symptom alleviating therapies, our small research program was able to adapt and produce results in the early days of the COVID-19 pandemic. While a variety of other COVID-19 studies took place at our institution across the pandemic, we made the explicit decision to give priority to clinical trials from the outset in

terms of support and preference. This was in part due to limited staffing; there were a finite number of potential trials we could offer our patient populations. However, what was delivered was executed expeditiously, with tight oversight from the research program and the IRB.

By providing ad-hoc IRB and ancillary review, and allocating investigator support from the hospital's tiny research department, we effectively brought our community access to clinical pharmaceutical trials, both as inpatients and via MIH, with appropriate patient protections, in a time of pandemic crisis. Our use of secure texting methods allowed us provide patients rapid access to compassionate use treatments. Moreover, this is a model that could be generalized to hospitals of any size in future pandemics.

Respectfully,



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Hello,

Thank you for the opportunity to provide input to OSTP on how best to operationalize protocol distribution and data capture for the upcoming RFI.

1. *Governance for emergency clinical trials response.*

a. Descriptions of models that could be used to establish a U.S.-level governance structure for emergency clinical trials. As noted above, one possible approach would be a centralized U.S.-level structure drawing membership from Federal agencies with relevant expertise.

- Today we have multisite/center trials with a "home base" or one hospital that is coordinating data and drug supply etc. The government could serve as this "home base" using hospitals and pharmacies as the extended sites.

b. Criteria that should be applied in determining when coordinated and potentially large-scale clinical research is needed to address an outbreak of disease or other biological incident, including signals or indicators that should be taken into account.

- When there is no approved form of therapy and lacking evidence based data.

c. Once a need for emergency clinical research is determined, factors relating to the outbreak or incident (*e.g.,* scope, location, severity) that should be considered in determining what types of studies are needed.

- Scope, location and severity along with pathogenicity and rate of transmission. Impact to our economic and social infrastructure.

d. Methods for communicating the decision to begin emergency clinical research to institutions and clinical trial networks that can participate in carrying out the research.

- NIH and clinicaltrials.gov feed many current sites with approved research information. Professional societies / groups focused on research and trials can also be engaged.

e. Mechanisms for tracking institutions, networks and sites that might be able to participate in emergency research, to ensure adequate potential for enrollment and adequate geographic coverage, domestically and internationally.

- IRB registry to have visibility into each IRB's reach and capabilities. Online annual surveys or reporting to collect specific information.

i. Criteria for establishing a target number and location of sites needed to support clinical trials in case of emergency.

- Diverse participants that cover the national population base meeting required sample size to power the study.

f. Procedures whereby the U.S. Government, together with external stakeholders, could oversee the development of clinical trial protocols and, where appropriate, the selection of investigational agents. It would be particularly helpful to get input on whether there is a role for public-private partnerships in this context.

- Development of a "hub-and-spoke" network arrangement between government and community health care providers.

g. Best practices, including "quality by design" principles, for designing trials so that they capture the data needed without unnecessary complexity that can complicate execution.

- CTTI quality by design project CTTIQUALITYBYDESIGNPROJECT--CRITICALTOQUALITY(CTQ)FACTORSPRINCIPLESDOCUMENT (ctti-clinicaltrials.org)

h. Best practices for designing trials that can enroll vulnerable populations, such as the pediatric population, as needed in particular circumstances.

- Broadening eligibility criteria both demographic characteristics of study populations (sex, race, ethnicity, age, location of residency) and non-demographic characteristics of populations (patients with organ dysfunction, comorbid conditions, disabilities, those at the extremes of the weight range, and populations with diseases or conditions with low prevalence)

i. Optimal ways to manage interactions with domestic and international regulatory bodies.

- HHS and OHRP working with international counterparts

j. Appropriate entities to handle projecting and tracking enrollment at study sites, monitoring the progress of clinical trials, and data management; whether existing entities could be engaged or adapted to carry out these functions for coordinated, large-scale emergency clinical trials.

- Development of a “hub-and-spoke” network arrangement between government and community health care providers, with the government serving as “home base” the extended sites could carry out these functions.

k. Appropriate ways to structure a data repository and a biorepository for emergency clinical trial data and specimens. As noted above, one potential model would be to collect data and biospecimens in centralized repositories. We would also appreciate input on whether existing entities could be engaged or adapted to handle these repository functions.

- In a “hub-and-spoke” network, the hubs could be adapted to handle these repository functions as they would in other research scenarios.

l. Criteria that should be applied to govern researchers' access to emergency clinical trial research data.

- Medical professional status and completion of basic clinical trial competencies.

Thank you again,
Al

Dr. Alfred Adam L’Altrelli, PharmD.
Senior Director of Pharmacy
UPMC Presbyterian-Shadyside
Adjunct Professor, School of Pharmacy
University Of Pittsburgh

Written response to:
White House Office for Science and Technology Policy
Clinical Research Infrastructure and Emergency Clinical Trials

Martin Landray, Stefan Gold and Nicholas Medhurst,
Good Clinical Trials Collaborative Coordinating Centre,
Protas[1], London, UK. www.goodtrials.org
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Contents

Recommendations

1. **Prioritize good trial design:** Key systemic actors (e.g. funders, regulators, commercial and non-commercial sponsors, and academia) should prioritise, support, reward and enable well-designed trials (and actively disincentivize studies with poor design).

2. **Adopt and implement principles-based clinical trial guidance:** The FDA, NIH and other government / government-funded organizations should adopt and apply the Guidance on Good Randomized Controlled Trials (RCTs) co-developed by diverse stakeholders as part of the Good Clinical Trials Collaborative. Such guidance is based on the fundamental scientific and ethical principles of good RCTs, fosters innovation in trial design and delivery, and provides flexibility to meet the (unpredictable) needs of changing circumstances such as those seen in the context of a pandemic.

3. **Fit-for-purpose infrastructure:** U.S. Government should undertake process optimization research to identify barriers to, and necessary infrastructural features of, large-scale RCTs that are common across health issues. This should consider the people, skills, processes, partnerships, data & technology required to establish and operate high quality RCTs at speed and at scale (including diversity in populations, geography, health setting, and disease features).

[1] Protas is a not-for-profit clinical trials organization focussed on enabling smarter clinical trials for better public health. www.protas.co.uk

The findings of such process optimization research should be implemented as soon as possible in order to ensure improvements are in place well in advance of the next public health emergency. It is as important (and cheaper) to stop wasteful or ineffective practices as to institute new ones.

4. **Preparation through useful practice:** Between public health emergencies, 'warm base' RCT infrastructure (people, processes, partnerships, data & technology) should be employed to generate high-quality evidence through an ongoing diverse portfolio of good trials across common health issues in non-communicable diseases, mental health, and infections.

5. **Public-private finance and partnership:** U.S. Government should invest public funds to generate the necessary infrastructure to support high quality RCTs. Industry, academia and health service providers should be encouraged to make use of that infrastructure for trials of novel products, re-purposed treatments, and to address uncertainties in the use of existing therapies. Attractive features of this approach would be the opportunities for greater speed, scale, and inclusivity. However, to give confidence in this approach it will be necessary for FDA to demonstrate and communicate the acceptability of results generated by it.

The design crisis

A high quality randomized clinical trial is one that provides a useful (reliable, informative, actionable) answer to an important question. Without these, clinical practice and the response to a public health emergency is vulnerable to hope, hype and uninformed practice – effective interventions remain unrecognized or under-used whilst ineffective or harmful practices persist. Such an approach is bad for individual patients, bad for public health, and bad for public trust in the healthcare response.

Good design is critical to success. That design must encompass scientific and ethical principles and ensure that the trial is practical and efficient for those who take part in it (patients, clinicians, healthcare organizations).

The COVID-19 pandemic illustrated the design crisis: Around 19 out of every 20 clinical trials launched in response to the COVID-19 pandemic were not fit for purpose, suffering from poor design - foreseeable inadequacies in scientific quality (not randomized, insufficient size), practicality, and coordination[2]. Among the 1 in 20 that did aim for robust design and sufficient scale, many were slow to enrol or did not complete. As articulated by Zarin et al before the pandemic "From the perspective of researchers, this is a form of research inefficiency. But from the perspective of participants, preventable uninformativeness is a serious breach of trust and a violation of research ethics."[3]

The system must prioritise, support, reward and enable well-designed studies (and actively disincentivize poor design) in order to improve knowledge-generation capacity both for emergency situations and in pursuit of better public health in general.

A practical example is found in work done by the Gates Foundation's Design, Analyze, and Communicate (DAC) program[4], which helps the major global health research funder to consult with

[2] Bugin K, Woodcock J. Trends in COVID-19 therapeutic clinical trials. Nature Reviews Drug Discovery. 2021, 20(4):254-255. doi: 10.1038/d41573-021-00037-3

[3] Zarin DA, Goodman SN, Kimmelman J. Harms From Uninformative Clinical Trials. JAMA. 2019;322(9):813–814. doi:10.1001/jama.2019.9892

[4] *"Uninformative research" is the global health crisis you've never heard of*; https://www.gatesfoundation.org/ideas/articles/deworm3-clinical-trials-show-the-value-of-informed-research

grantees to improve the 'informativeness' (practice-guiding impact) of clinical trials that they fund. This is a proactive investment in optimizing research plans that can deliver substantial efficiencies while enhancing research quality.

Unless the design challenge is addressed, all other measures to improve the infrastructure and wider ecosystem are doomed to failure.

The need for principles-based guidance

It is not possible to confidently predict what the defining features of the next healthcare emergency will be (e.g. speed of outbreak, mortality) or what demands it will place on various components of the care pathway (e.g. diagnosis, community settings, hospital care). However, we do know that we will want and need robust evidence to guide policy decisions at the earliest opportunity, and guiding principles enable application of reliable methods even to entirely novel challenges.

Guidance that places undue emphases on adhering to current processes and current capabilities risks being unfit for future emergencies. Instead what is needed is a principles-based approach that accommodates and remains relevant to innovation in technologies and methods but also accommodates and remains relevant for application in as-yet-unknown emergency situations.

This need was summarised as a key action in the "100 Days Mission to Respond to Future Pandemic Threats" report from the G7:

> *We should refocus regulatory guidelines on the fundamental scientific and ethical principles that underpin randomised trials, whilst embracing flexibility and innovation across a range of health threats and technologies. We should build on models established by the US Food and Drug Administration Clinical Trial Transformation Initiative and the Good Clinical Trials Collaborative (supported by the Bill & Melinda Gates Foundation, Wellcome Trust, and African Academy of Science). The Good Clinical Practice for clinical trials guidance should be revised to focus on what matters for the generation of actionable information about effects of an intervention, rather than what is easy to check but less relevant, placing an emphasis on principles and purpose rather than process.*[5]

Building on the work of the Good Clinical Trials Collaborative

The work to develop such guidance has already been done. The **Good Clinical Trials Collaborative** (GCTC), a non-profit programme worked with a diverse, global multidisciplinary group of individuals and organizations to co-create guidance that was

- **Based on key scientific and ethical principles** and focused on issues that materially matter to the well-being of trial participants and the reliability of RCT results;
- **Clear, concise, consistent and proportionate to the context** and setting in which RCTs are conducted, recognizing that there are risks associated with both usual clinical practice and a lack of reliable evidence on the effects of an intervention;
- **Forward looking, fostering innovation in health interventions and trial methods**, including the appropriate use of routine healthcare data, technologies, and designs; and

5 https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/992762/100_Days_Mission_to_respond_to_future_pandemic_threats__3_.pdf

- **Flexible, widely applicable, utilizable and durable** across disease areas, intervention types, development phases, trial designs, geographies and time.

[Among the many contributors to the development of this guidance were senior and experienced figures from NIH, FDA, industry, academia, professional and patient organizations.]

Five key principles for Good Randomized Clinical Trials

The GCTC guidance sets out 5 key principles for good Randomized Clinical Trials. These are summarized below. For the full version and detailed explanations, please visit https://www.goodtrials.org/the-guidance/guidance-overview/

1. **Good trials are designed to produce scientifically sound answers to relevant questions.**

   Randomized clinical trials should help to resolve important uncertainties about effects of health interventions. Depending on the context, the results may be needed to determine whether to proceed with development or further evaluation of the intervention or to inform regulatory licensing, clinical guidelines, and/or health policy. In each case, any uncertainties applying to the specific question(s) that remain at the end of the RCT should be sufficiently small to allow meaningful decisions to be made. This requires the combination of: randomization, adequate sample size, unbiased assessment of outcomes, and intention-to-treat analyses.[6]

2. **Good trials respect the rights and well-being of participants**

   Randomized clinical trials should combine scientific validity with appropriate protection and respect for those who participate in them. These features are only possible to achieve with an emphasis on good communication and information sharing, consent, and management of the safety of those taking part.

3. **Good trials are collaborative and transparent**

   Potential participants and/or members of the relevant community provide valuable contributions to the design, execution and interpretation of RCTS. Working collaboratively across organizations and sectors (e.g. government, industry, academia, healthcare) provides diversity of thinking and supports a delivery approach that is appropriate to the context, efficient and resilient. Transparency - trial registration, publication of protocols, and prompt reporting of results for scientific and lay audiences – aids the development of trustworthiness.

4. **Good trials are designed to be feasible for their context**

   Randomized clinical trials should be tailored to be practicable given the available infrastructure in relevant settings. This includes making optimal use of pre-existing resources and facilities, including utilizing any expertise, skills, professional standards, and quality oversight mechanisms associated with routine healthcare practice. RCTs should not be wasteful of staff and participants' time, use of interventional or other medical supplies, energy, or environmental resources. Where there are strengths and safeguards in routine systems, these should not be duplicated or altered without careful justification. The closer trial processes are to routine practice for participants and staff, the more efficiently and effectively they are likely to be delivered and the fewer mistakes they are likely to make, resulting in improved quality.

[6] Collins R, Bowman L, Landray M, Peto R. The Magic of Randomization versus the Myth of Real-World Evidence. N Engl J Med. 2020 Feb 13;382(7):674-678. doi: 10.1056/NEJMsb1901642. PMID: 32053307.

5. Good trials manage quality effectively and efficiently

Planning for success requires focus on issues that matter – avoiding errors that would have a material impact on the well-being of the participants in the trial or the reliability of the results (which influence, directly or indirectly, the care of future patients outside the trial). Good quality should be prospectively built into the design and delivery rather than relying on retrospectively tring to detect issues after they occurred (when often they cannot be rectified). Monitoring, regulatory, auditing or inspection requirements should be proportionate and sensitive to the scientific and ethical qualities and objectives of a RCT. They should recognise the opportunity-cost of, and avoid, setting irrelevant or disproportionate requirements that might discourage the conduct or participation in good RCTs that are designed to address important questions.

Just as good trials should manage quality effectively and efficiently, so too should those who fund, deliver, oversee or regulate those trials.

Streamlining and quality are not opposed

Senior leaders at FDA have made clear:

> Streamlining *and quality are not opposed; rather, by applying quality-by-design principles, reliable evidence can be developed with planned, measurable quality when researchers focus on ensuring both the quality of data that address important research questions and trial conduct that protects patient safety. Providing incentives for such approaches could accelerate development of information on drug effectiveness and safety, giving US clinicians and patients earlier access to critical knowledge* and advancing public health.[7]

To achieve appropriate scale, speed and efficiency, care must be taken to remove unnecessary barriers to broad participation of patients/members of the public, clinical staff, and healthcare organizations.[8] Prioritising development and maintenance of systems that enable broad efficiencies (e.g multi-centre ethics reviews and accessible IT and data systems) is another key driver of feasibility and efficiency. Investing in such systems as a common public good can help deliver a 'warm base' environment that serves all trials and public health.

Avoiding pandemic amnesia and emergency exceptionalism

It is easy to dismiss the failures of the COVID-19 pandemic (the multiple designed-to-fail studies and widespread adoption of hope- rather than evidence-based medicine) as aberrations in an otherwise functioning system. Likewise it is easy to assume that the successes (e.g. RECOVERY, REMAP-CAP, ACTIV, SOLIDARITY trials) can be readily repeated without the need for system transformation. In many ways, the only two things that are 'special' about the public health emergency settings are the clarity of focus (COVID-19 was the only item on the agenda in early 2020) and the pressing need for speed.

However, most of the challenges experienced in conducting clinical trials in public health emergencies are not unique to emergency situations, and the greatest value and efficiency can be achieved by understanding and overcoming common barriers to delivering good trials.

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[7] Califf RM, Cavazzoni P, Woodcock J. Benefits of Streamlined Point-of-Care Trial Designs: Lessons Learned From the UK RECOVERY Study. *JAMA Intern Med.* 2022;182(12):1243–1244. doi:10.1001/jamainternmed.2022.4810

[8] Pessoa-Amorim G, Campbell M, Fletcher L, Horby P, Landray M, Mafham M, Haynes R. Making trials part of good clinical care: lessons from the RECOVERY trial Future Healthc J Jul 2021, 8 (2) e243-e250; DOI: 10.7861/fhj.2021-0083

Two critical questions can help focus the lens of this White House OSTP initiative: (1) What is special or different (from routine care) about running a clinical trial? And (2) what is special or different (from trials between pandemics) about a clinical trial that is part of an emergency response?

It is important to identify and address policies, processes and incentives that inappropriately or disproportionately hamper the generation of sound evidence from RCTs whilst allowing evidence-free practice to run free.

Avoiding emergency exceptionalism also means that a 'warm base' infrastructure is built through ongoing delivery of active research projects that include non-communicable diseases and infectious diseases.

The US (like other health systems worldwide) is faced with the twin challenges of growing burden of common disease and escalating cost of the impact that has on individuals, their families, health systems, the economy and wider society. There is a pressing need for more a more efficient evidence-generation approach through the application of large-scale randomized controlled trials to evaluate ways to prevent and treat common health conditions, such as cardiovascular disease, diabetes, mental health, dementia and drug-resistant infection.

At the heart of this approach sits the need for all those who fund, support, conduct and regulate clinical trials to focus on the fundamental principles of good randomized clinical trials.

Success-by-design

Success comes from good design, ongoing practice, and application of lessons learned supported by infrastructure (skilled people, efficient processes, effective partnerships, and accessible data & technology) all focused on the issues that have a material influence on the generation of useful (reliable, informative, actionable) answers to relevant questions.

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About the Good Clinical Trials Collaborative (GCTC)

The Good Clinical Trials Collaborative, established in 2020, is a non-profit organization focused on developing and promoting new guidance to enable better randomized controlled trials (RCTs) globally. It is led by Professor Sir Martin Landray, co-architect of the Covid-19 RECOVERY trial and supported by Wellcome and the Bill & Melinda Gates Foundation.

Guided by the belief that good healthcare is informed by good evidence from good trials, the Collaborative's objective is to make it easier to do good RCTs with new guidance that sets an international benchmark of scientific rigor, ethical integrity, efficiency and quality.

The new guidance is available at https://www.goodtrials.org/ and was developed through collaboration with a diverse, multidisciplinary group of individuals and organizations with a shared commitment to help accelerate better healthcare across the world. Outlining the five underpinning principles of good RCTs, the guidance is intended to support all parties involved with RCTs of all types of health interventions, in all settings.

EMORY
ROLLINS SCHOOL OF PUBLIC HEALTH
Department of Biostatistics and Bioinformatics

January 23, 2022

Office of Science and Technology Policy (OSTP)
emergencyclinicaltrials@ostp.eop.gov
RE: Request for Information; Clinical Research Infrastructure and Emergency Clinical Trials

For the committee's consideration,

My name is Natalie Dean, PhD. I am an Assistant Professor in the Department of Biostatistics & Bioinformatics and in the Department of Epidemiology at Emory University's Rollins School of Public Health. I am submitting a comment in response to this RFI as an individual.

As background, my research focuses on the evaluation of vaccines during public health emergencies. I previously worked on a Phase 3 vaccine trial of the rVSV-ZEBOV vaccine for Ebola (Henao-Restrepo et al. 2015; Henao-Restrepo et al. 2017). The trial used an innovative ring vaccination design tailored to outbreak setting (Ebola ca Suffit Ring Vaccination Trial 2015; Dean and Longini 2022). I subsequently worked with the World Health Organization's R&D Blueprint Initiative, on the working group on clinical trials norms and standards (Bellan et al. 2019; Dean et al. 2019). In particular, we considered the challenges of pathogens that cause outbreaks of unpredictable size and duration, and the role of core (master) protocols to expand trials into new locations, enabling the accrual of data on a rolling basis (Dean et al. 2020a). I am Principal Investigator on an NIH/NIAID R01 awarded in 2018 on the topic of "Design and Analysis of Vaccine Trials for Emerging Infectious Disease Threats" (R01-AI139761). We have further considered the role of mathematical and statistical modeling for guiding site selection and sample size decisions for vaccine trials (Dean et al. 2020b; Madewell et al. 2021a; Madewell et al. 2021b). I am currently working with partners to apply these strategies to a chikungunya vaccine trial and, in the future, a Lassa vaccine. During the COVID-19 pandemic, I was active in public engagement, writing op-eds to explain clinical trial design to the readers of the *Washington Post* and *New York Times*, and advocated for better coordination of clinical trial and study designs (Kimmel et al. 2020; Ogburn et al. 2020; Dean 2021).

I am highly interested in the topic of clinical research infrastructure and emergency clinical trials, and I have two comments to offer to the committee in response to this request for information. These comments identify areas that I believe merit further consideration by the committee, which I did not see mentioned explicitly in the RFI or during the panel discussion. The comments respond most closely to Topic 1. "Governance for emergency clinical trials response" and Topic 6. "International coordination and capacity."

1. **Complex decision-making in clinical trials**

While a randomized clinical trial is ongoing, new information is constantly emerging that has implications for the ongoing trial. This is true for many types of clinical trials, but is particularly true in the context of an emerging infectious disease outbreak. In an epidemic, the situation is fast-evolving, and there may be multiple other trials running in parallel evaluating the same or similar interventions. While one of the important aims of this RFI is to increase trial coordination, for an outbreak that is widespread enough, inevitably there will be some redundancy. This leads to practical questions. If trial A of treatment X is ongoing, and independent trial B demonstrates a clinically meaningful benefit of treatment X for the same or similar population, how should this impact trial A? How does this depend upon characteristics of trial B? Is it necessary for trial A to fully replicate the results of trial B? Relatedly, one can imagine a setting where neither trial A nor trial B are sufficiently large to demonstrate a benefit independently, but combined there is enough information. Combining trial data in this way is something our group has explored from a statistical point of view (unpublished, available to discuss further), yet many questions remain about best practices. In the context of the pandemic, the scientific community saw this play out with the decision to merge ongoing, independent trials of the AstraZeneca/Oxford vaccine to achieve a faster result, even despite differences in their design and population (Voysey et al. 2021).

This evolving landscape places a unique burden on DSMBs, as strategies to handle information external to the trial may be difficult or impossible for the investigators to fully pre-specify. Thus, one area for development is how external information flows into a DSMB to guide decision-making, and strategies to formalize these data sharing processes so they are timely and useful. One of the advantages of a shared Data and Safety Monitoring Board (DSMB) for the Operation Warp Speed vaccine trials was the ability to use a safety signal from one trial as a trigger to explore safety data in other trials (Joffe et al. 2021). Furthermore, there should be greater agreement from across the scientific committee about how external information should be handled for decisions about data accrual and analysis. Finally, how does information flow back out of the trial to guide other trials and committees charged with coordinating and prioritizing

other research activities, as all are part of the same larger cycle. These all merit further discussion.

2. Addressing incentive structures in academia

As is well-recognized by the committee, the emergence of so many underpowered and redundant trials early on in the pandemic was a waste of resources, effort, and time (Bugin and Woodcock 2021). The root causes for this situation were surely many. Investigators launched into action during a crisis, and with an accelerated timeline and without established networks and data sharing agreements, many went ahead alone (and received funding to do so). Yet this was short-term thinking as the larger networks, once they were rolling, were far more successful.

Again, these challenges are well-recognized by the committee. My comment to add is to make sure that the investigation into the root causes includes the concept of "credit," particularly for investigators at academic medical institutions. There are strong incentive structures to be the lead author or Principal Investigator on a large, life-saving discovery. In contrast, there is less reward for being a member of a large consortium. Yet large consortiums are far better positioned to generate life-saving discoveries. This relates to ongoing discussions about how academia rewards other types of activities, like data generation, data curation, sharing code, and maintaining dashboards and tools (Kucharski, Funk, and Eggo 2020). Thus, an area for study is the model for promotion for academic researchers and how this can better align with collaborative research models and the growing "team science" movement.

I hope these comments are helpful to the committee. I am very interested in this important line of work, and I would be honored to contribute further as the committee sees fit.

Sincerely,

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References:

Bellan, S. E., Eggo, R. M., Gsell, P. S., Kucharski, A. J., Dean, N. E., Donohue, R., Zook, M., Edmunds, W. J., Odhiambo, F., Longini, I. M., Jr., Brisson, M., Mahon, B. E., and Henao-Restrepo, A. M. (2019), "An online decision tree for vaccine efficacy trial design during infectious disease epidemics: The InterVax-Tool," *Vaccine*, 37 (31), 4376-4381. DOI: 10.1016/j.vaccine.2019.06.019.

Bugin, K., and Woodcock, J. (2021), "Trends in COVID-19 therapeutic clinical trials," *Nature Reviews Drug Discovery*, 20 (4), 254-255. DOI: 10.1038/d41573-021-00037-3.

Dean, N. (2021), "COVID vaccination studies: plan now to pool data, or be bogged down in confusion," *Nature*, 591 (7849), 179. DOI: 10.1038/d41586-021-00563-5.

Dean, N. E., Gsell, P. S., Brookmeyer, R., Crawford, F. W., Donnelly, C. A., Ellenberg, S. S., Fleming, T. R., Halloran, M. E., Horby, P., Jaki, T., Krause, P. R., Longini, I. M., Mulangu, S., Muyembe-Tamfum, J. J., Nason, M. C., Smith, P. G., Wang, R., Henao-Restrepo, A. M., and De Gruttola, V. (2020a), "Creating a Framework for Conducting Randomized Clinical Trials during Disease Outbreaks," *N Engl J Med*, 382 (14), 1366-1369. DOI: 10.1056/NEJMsb1905390.

Dean, N. E., Gsell, P. S., Brookmeyer, R., De Gruttola, V., Donnelly, C. A., Halloran, M. E., Jasseh, M., Nason, M., Riveros, X., Watson, C. H., Henao-Restrepo, A. M., and Longini, I. M. (2019), "Design of vaccine efficacy trials during public health emergencies," *Sci Transl Med*, 11 (499). DOI: 10.1126/scitranslmed.aat0360.

Dean, N. E., and Longini, I. M. (2022), "The ring vaccination trial design for the estimation of vaccine efficacy and effectiveness during infectious disease outbreaks," *Clin Trials*, 19 (4), 402-406. DOI: 10.1177/17407745211073594.

Dean, N. E., Pastore, Y. P. A., Madewell, Z. J., Cummings, D. A. T., Hitchings, M. D. T., Joshi, K., Kahn, R., Vespignani, A., Halloran, M. E., and Longini, I. M., Jr. (2020b), "Ensemble forecast modeling for the design of COVID-19 vaccine efficacy trials," *Vaccine*, 38 (46), 7213-7216. DOI: 10.1016/j.vaccine.2020.09.031.

Ebola ca Suffit Ring Vaccination Trial, C. (2015), "The ring vaccination trial: a novel cluster randomised controlled trial design to evaluate vaccine efficacy and effectiveness during outbreaks, with special reference to Ebola," *BMJ*, 351, h3740. DOI: 10.1136/bmj.h3740.

Henao-Restrepo, A. M., Camacho, A., Longini, I. M., Watson, C. H., Edmunds, W. J., Egger, M., Carroll, M. W., Dean, N. E., Diatta, I., Doumbia, M., Draguez, B., Duraffour, S., Enwere, G., Grais, R., Gunther, S., Gsell, P. S., Hossmann, S., Watle, S. V., Konde, M. K., Keita, S., Kone, S., Kuisma, E., Levine, M. M., Mandal, S., Mauget, T., Norheim, G., Riveros, X., Soumah, A., Trelle, S., Vicari, A. S., Rottingen, J. A., and Kieny, M. P. (2017), "Efficacy and effectiveness of an rVSV-vectored vaccine in preventing Ebola virus disease: final results from the Guinea ring vaccination, open-label, cluster-randomised trial (Ebola Ca Suffit!)," *Lancet*, 389 (10068), 505-518. DOI: 10.1016/S0140-6736(16)32621-6.

Henao-Restrepo, A. M., Longini, I. M., Egger, M., Dean, N. E., Edmunds, W. J., Camacho, A., Carroll, M. W., Doumbia, M., Draguez, B., Duraffour, S., Enwere, G., Grais, R., Gunther, S., Hossmann, S., Konde, M. K., Kone, S., Kuisma, E., Levine, M. M., Mandal, S., Norheim, G., Riveros, X., Soumah, A., Trelle, S., Vicari, A. S., Watson, C. H., Keita, S., Kieny, M. P., and Rottingen, J. A. (2015), "Efficacy and effectiveness of an rVSV-vectored vaccine expressing Ebola surface glycoprotein: interim results from the Guinea ring vaccination cluster-randomised trial," *Lancet*, 386 (9996), 857-866. DOI: 10.1016/S0140-6736(15)61117-5.

Joffe, S., Babiker, A., Ellenberg, S. S., Fix, A., Griffin, M. R., Hunsberger, S., Kalil, J., Levine, M. M., Makgoba, M. W., Moore, R. H., Tsiatis, A. A., and Whitley, R. (2021), "Data and Safety Monitoring of COVID-19 Vaccine Clinical Trials," *J Infect Dis*, 224 (12), 1995-2000. DOI: 10.1093/infdis/jiab263.

Kimmel, S. E., Califf, R. M., Dean, N. E., Goodman, S. N., and Ogburn, E. L. (2020), "COVID-19 Clinical Trials: A Teachable Moment for Improving Our Research Infrastructure and Relevance," *Ann Intern Med*, 173 (8), 652-653. DOI: 10.7326/M20-2959.

Kucharski, A. J., Funk, S., and Eggo, R. M. (2020), "The COVID-19 response illustrates that traditional academic reward structures and metrics do not reflect crucial contributions to modern science," *PLOS Biology*, 18 (10). DOI: 10.1371/journal.pbio.3000913.

Madewell, Z. J., Dean, N. E., Berlin, J. A., Coplan, P. M., Davis, K. J., Struchiner, C. J., and Halloran, M. E. (2021a), "Challenges of evaluating and modelling vaccination in emerging infectious diseases," *Epidemics*, 37, 100506. DOI: 10.1016/j.epidem.2021.100506.

Madewell, Z. J., Pastore, Y. P. A., Zhang, Q., Burton, N., Yang, Y., Longini, I. M., Halloran, M. E., Vespignani, A., and Dean, N. E. (2021b), "Using simulated infectious disease outbreaks to inform site selection and sample size for individually randomized vaccine trials during an ongoing epidemic," *Clin Trials*, 18 (5), 630-638. DOI: 10.1177/17407745211028898.

Ogburn, E. L., Bierer, B. E., Brookmeyer, R., Choirat, C., Dean, N. E., De Gruttola, V., Ellenberg, S. S., Halloran, M. E., Hanley, D. F., Jr., Lee, J. K., Wang, R., and Scharfstein, D. O. (2020), "Aggregating data from COVID-19 trials," *Science*, 368 (6496), 1198-1199. DOI: 10.1126/science.abc8993.

Voysey, M., Clemens, S. A. C., Madhi, S. A., Weckx, L. Y., Folegatti, P. M., Parvinder, K. A., Angus, B., Baillie, V. L., Barnabas, S. L., Bhorat, Q. E., Bibi, S., Briner, C., Cicconi, P., Collins, A. M., Colin-Jones, R., Cutland, C. L., Darton, T. C., Dheda, K., Duncan, C. J. A., Emary, K. R. W., Ewer, K. J., Fairlie, L., Faust, S. N., Feng, S., Ferreira, D. M., Finn, A., Goodman, A. L., Green, C. M., Green, C. A., Heath, P. T., Hill, C., Hill, H., Hirsch, I., Hodgson, S. H., Izu, A., Jackson, S., Jenkin, D., Joe, C. C. D., Kerridge, S., Koen, A., Kwatra, G., Lazarus, R., Lawrie, A. M., Lelliott, A., Libri, V., Lillie, P. J., Mallory, R., Mendes, A. V. A., Milan, E. P., Minassian, A. M., McGregor, A., Morrison, H., Mujadidi, Y. F., Nana, A., O'Reilly, P. J., Padayachee, S. D., Pittella, A., Plested, E., Pollock, K. M., Ramasamy, M. N., Rhead, S., Schwarzbold, A. V., Singh, N., Smith, A., Song, R., Snape, M. D., Sprinz, E., Sutherland, R. K., Tarrant, R., Thomson, E. C., Torok, M. E., Toshnoer, Turner, D. P. J., Vekemans, J., Villafana, T. L., Watson, M. E. E., Williams, C. J., Douglas, A. D., Hill, A. V. S., Lambe, T., Gilbert, S. C., and Pollard, A. J. (2021), "Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK," *The Lancet*, 397 (10269), 99-111. DOI: 10.1016/s0140-6736(20)32661-1.

TranspariMED
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Bristol, UK, 31 October 2022

Clinical Research Infrastructure and Emergency Clinical Trials

About this submission

This submission is being made in response to the "Notice of Request for Information (RFI) on clinical research infrastructure and emergency clinical trials" issued by OSTP on 19 October 2022.
https://www.govinfo.gov/content/pkg/FR-2022-10-26/pdf/2022-23110.pdf
[FR Doc. 2022–23110 Filed 10–25–22; 8:45 am]
BILLING CODE 3270–F1–P

About the submitter

TranspariMED, a global non-profit initiative to end evidence distortion in medicine, has five years' experience in working to improve clinical trial regulation worldwide, including in the U.S., with a particular focus on clinical trial registries. We are open to further exchanges with OSTP and other U.S. stakeholders on the issues discussed below.

Clinical Research Infrastructure and Emergency Clinical Trials

1a. Descriptions of models that could be used to establish a U.S.-level governance structure for emergency clinical trials. As noted above, one possible approach would be a centralized U.S.-level structure drawing membership from Federal agencies with relevant expertise.

From an operational risk management perspective, it may be better to have 2-3 separate U.S. trial networks (possibly all using the same inclusion/exclusion criteria and endpoints) than a single national mega-trial. For example, WHO's SOLIDARITY Covid trial took far longer than expected to get off the ground in practice.

1f. Procedures whereby the U.S. Government, together with external stakeholders, could oversee the development of clinical trial protocols and, where appropriate, the selection of investigational agents.

Key actors to involve are WHO and ICRMA. Not every trial globally would need to pursue the same small number of investigational agents. For example, some researchers thought that corticosteroids should not be included in RECOVERY. It would have been a tragedy if all Covid trials worldwide had excluded that drug due to a centralised approach.

1j. Appropriate entities to handle projecting and tracking enrollment at study sites, monitoring the progress of clinical trials, and data management; whether existing entities could be engaged or adapted to carry out these functions for coordinated, large-scale emergency clinical trials.

The global ICTRP trial registry system already provides an adequate framework for this, but it was not well used during Covid. The entity running an emergency trial should be required to update the registry entry on a monthly basis with current enrolment figures, both overall and for each study arm: https://www.transparimed.org/single-post/covid-clinical-trial-registr
The leading U.S. expert on this is Deborah Zarin, former ClinicalTrials.gov administrator.

ii. Publication/accessibility of trial data, including availability of data prior to publication and publication rights.

Again, the global trial registry system already provides an adequate framework for this, but it was rarely used during Covid. ClinicalTrials.gov allows the rapid uploading of tabular summary results, with NLM staff providing quality control. Thus, trial registries combine the strengths of preprints (speed) with those of peer-reviewed publications (quality control). See:
https://www.transparimed.org/single-post/2019/04/24/why-is-uploading-clinical-results-onto-trial-registries-so-important

Note that the European Medicines Agency (EMA) has adopted new rules for disclosing the results of trials on registries specifically during public health emergencies. Like the FDA (FDAAA Section 801), EMA usually requires trial results to be made available on a registry within 12 months of trial completion. As this is too slow in a public health emergency, EMA may by law during future emergencies tighten the reporting timeline for relevant trials. The new legislation leaves open by how much EMA may tighten the timeline, which is wise as technology and hence feasibility constantly evolve. The next pandemic may only strike in 30 years, so reporting timelines should be decided upon then, rather than being cast in stone on the basis of 2022 technology and processes.

iii. Use of a single IRB across all participating trial sites. As a related point, it would be helpful to get feedback on whether an IRB should be established that is primarily devoted to emergency clinical trials.

The Health Research Authority (HRA) in the UK oversaw very rapid and thorough ethics approvals during Covid. Crucially, HRA also refused ethics approval for trials that fell outside the parameters of national Covid research priorities, and so avoided the fragmentation of resources and patients between many small trials. Contact Naho Yamasaki from HRA for lessons learned.

6. International coordination and capacity. a. Designing the overall domestic emergency clinical trials effort in a way that coordinates with international clinical research efforts. It would be helpful to receive comments on how to facilitate the participation of foreign-run clinical trial networks and other foreign bodies in coordinated, large-scale emergency clinical trial protocols initiated by the U.S.

First and foremost, “initiated by the US” is probably not the best starting point, especially considering that the US did not exactly excel at this during Covid. Protocol alignment should be coordinated with WHO and ICRMA, but in order to better manage implementation risk, it may be wiser to run trials separately in different jurisdictions on an operational level, and only pool the results of different trials using identical end points post hoc.

Note also that the course of pandemics in unpredictable, some regions may have far higher case numbers than others; part of the reason that RECOVERY was able to deliver insights so rapidly was the high number of Covid cases specifically in the UK, which nobody could have predicted.

One option that could be explored is a single global Data Safety and Monitoring Board (DSMB) for all aligned trials that is able to periodically preview the preliminary data generated by multiple trials.

c. Overcoming regulatory barriers that delay expansion of U.S. trials into international sites, or otherwise interfere with clinical research across borders.

A review of the experiences of the SOLIDARITY Covid trial may be useful for this. Also, dialogue with the EMA because efforts to coordinate Covid trials across Europe were largely unsuccessful; a new long-term EMA programme (ACT-EU) is currently trying to overcome these barriers.

d. The best way to track the clinical trial research initiatives being pursued under the G7 Trials Charter and Quad leaders' commitment to pandemic preparedness, and to harmonize U.S. emergency clinical trials efforts with these international initiatives.

The existing global clinical trial registry infrastructure already makes it possible to gain a comprehensive overview of global research efforts, but it has been undermined by weak regulatory and funding engagement:
https://www.transparimed.org/single-post/covid-clinical-trial-registr

Instead of re-inventing the wheel, regulators in key countries should put into place systems that ensure that all trials are pre-registered, registry data regularly updated, and results promptly made public on ICTRP contributing trial registries, as per existing WHO best practices.

A good first step would be for FDA to finally track and enforce compliance with FDAAA Section 801, and for NIH to track and enforce compliance with its own trial registration and reporting requirements.
https://www.transparimed.org/single-post/massachusetts-general-hospital-clinical-trials
https://www.transparimed.org/single-post/oig-report-nih-clinical-trials

Experience shows that institutions can only consistently comply with reporting requirements if they have adequate systems in place, i.e. these systems have to be set up long before a pandemic strikes. FDA and NIH enforcement now would ensure that all U.S. institutions set up such systems.

The 2022 WHA Clinical Trials Resolution and the 2017 WHO Joint Statement provide useful frameworks for global harmonisation, including via trial registries.
https://www.transparimed.org/single-post/who-consultation-clinical-trials-resolution
https://www.who.int/news/item/18-05-2017-joint-statement-on-registration

In the context of public health emergencies, the timelines for updating registry entries and uploading trial results will have to be tightened beyond current WHO benchmarks, and regulators such as FDA and public funders such as NIH will have to proactively track and promote compliance.

[DOCUMENT ENDS]

Society for Women's Health Research

January 27, 2023

Arati Prabhakar
Director
White House Office of Science and Technology Policy
Washington, D.C. 20500

Comments submitted electronically to emergencyclinicaltrials@ostp.eop.gov.

Re: OSTP Request for Information (87 FR 64821); Clinical Research Infrastructure and Emergency Clinical Trials

Dear Director Prabhakar:

The Society for Women's Health Research (SWHR), a more than 30-year-old national nonprofit dedicated to promoting research on biological sex differences in disease and improving women's health through science, policy, and education, is pleased to offer comments in response to the Office of Science and Technology Policy (OSTP) Request for Information (RFI): Clinical Research Infrastructure and Emergency Clinical Trials.

As an organization whose work and mission revolves around the representation of women and subpopulations of women in clinical trials and supporting these populations in areas, including federal policy, SWHR appreciates that OSTP—in partnership with the National Security Council (NSC)—recognizes the role of clinical trials in responding to outbreaks of disease and other emergencies as well as the importance of ensuring that there is diversity within these clinical trials and among clinical investigators. Guaranteeing that our federal research infrastructure has the capacity to respond to such situations in the future is vital for protecting the health, well-being, and safety of all Americans.

As OSTP and NSC explore ways to enhance U.S. clinical trial infrastructure, SWHR would like to raise the following items for consideration.

I. **Ensure the Inclusion of Pregnant and Lactating Populations in Clinical Trials**

SWHR implores OSTP and NSC to ensure that the U.S. clinical trial infrastructure prioritizes the inclusion of pregnant and lactating populations in clinical research, including during times of emergency. The failure to include these populations in trials can lead to harmful gaps in evidence for both mother and baby.

During a recent webinar hosted by the Coalition to Advance Maternal Therapeutics (CAMT), for which SWHR serves as the administrator, panelist Anne Lyerly, MD, MA,

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a professor in the School of Medicine at the University of North Carolina, Chapel Hill discussed the negative unintended downstream effects of excluding pregnant populations from clinical trials. Specifically, she noted that without adequate evidence, pregnant persons may be given drugs at the wrong dose, resulting in either exposure to disease (when dosed too low) or toxicity (when dosed too high); may be given drugs with unacceptable risk; or may be denied access to beneficial drugs.

The COVID-19 pandemic served as a stark reminder of this unnecessary reality. Due to the exclusion of pregnant populations in early COVID-19 clinical trials, women and their health care providers were left to make decisions about whether to get the COVID-19 vaccine without any kind of data to support their decision. This left women and their children vulnerable and their health care providers at risk of making an incalculable recommendation. Further, the absence of data likely allowed vaccine hesitancy to grow and misinformation to proliferate. In other words, this exclusion was dangerous at both an individual and population level.

As we now know from mounting evidence,[1] the COVID-19 vaccine *is* safe and effective for pregnant and breastfeeding populations and is not, as early speculations indicated, associated with fertility problems. Further, data has shown pregnant women and women who were recently pregnant are more likely to get severely ill from COVID-19, demonstrating the harm that can result from women not being vaccinated against the virus. Including pregnant and lactating women at the outset of these trials would have led to having this beneficial information sooner, and thus resulted in better outcomes for mothers and babies across the country sooner.

SWHR supports incorporating pregnant and lactating populations at every level of our federal research infrastructure. This includes, but is not limited to, identifying ways to increase recruitment among these populations, ensuring that the workforce of clinicians and researchers include those with expertise in obstetric and lactation pharmacology and therapeutics, and providing incentives or financial support to those sites that enroll these populations.

II. Enhance Representation of Underrepresented Populations in the Research Workforce

African Americans, Hispanics, Native American/Alaska Natives, and Native Hawaiian/Pacific Islanders are expected to form more than half of the U.S.

[1] Safety and Effectiveness of COVID-19 Vaccination During Pregnancy. COVID-19 Vaccines While Pregnant or Breastfeeding, Centers for Disease Control and Prevention. https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/pregnancy.html#anchor_1628692520287 Accessed 26 January 2023.

population by 2050.[2] However, these populations, along with women and people with disabilities, remain underrepresented in the biomedical workforce.[3]

SWHR strongly believes that having more diverse research teams results in better science. Research has shown that having more diversity among researchers can help promote trust toward precision medicine research[4] and that research is of higher quality with diverse teams in place.[5] Therefore, ensuring that our federal research infrastructure prioritizes the recruitment and retention of a diverse biomedical research workforce is of critical public health importance. It is through a diverse workforce that we can better reflect the perspectives of all populations and their unique health needs, including in, but not limited to, times of emergency.

SWHR encourages OSTP and NSC to ensure that underrepresented minority populations are fully integrated within the research workforce and to take steps to increase the involvement of these populations, including:

a. Integrating strategies to improve representation across the educational and institutional systems that exist for training, funding, executing, and publishing research;
b. Encouraging federal research institutions to continue assessing the barriers to equity that exist within them and actively engaging to correct course; and
c. Prioritizing opportunities for underrepresented minorities for mentoring, coaching, and collaborating with principal investigators who have federal funding.[6]

III. **Supporting Participation of Different Communities Through Clinical Trial Site Locations**

Finally, as mentioned within the RFI, conducting clinical trials during a national emergency will involve needing to establish trial sites across the country. As OSTP and NSC explore the target number and location of various sites, it will be vital to consider how to best promote access to these sites for a diversity of populations.

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[2] Vishwanatha JK, Basha R, Nair M, Jones HP. An Institutional Coordinated Plan for Effective Partnerships to Achieve Health Equity and Biomedical Workforce Diversity. *Ethnicity & Disease*. 2019;29(Suppl 1):129.
[3] Ibid.
[4] Kraft SA, Cho MK, Gillespie K, Halley M, Varsava N, Ormond KE, Luft HS, Wilfond BS, Soo-Jin Lee S. Beyond Consent: Building Trusting Relationships With Diverse Populations in Precision Medicine Research. Am J Bioeth. 2018 Apr;18(4):3-20. doi: 10.1080/15265161.2018.1431322. PMID: 29621457; PMCID: PMC6173191.
[5] Campbell LG, Mehtani S, Dozier ME, Rinehart J. Gender-heterogeneous working groups produce higher quality science. PLoS One. 2013 Oct 30;8(10):e79147. doi: 10.1371/journal.pone.0079147. PMID: 24205372; PMCID: PMC3813606.
[6] Hemming J, Eide K, Harwood E, et al. Exploring Professional Development for New Investigators Underrepresented in the Federally Funded Biomedical Research Workforce. *Ethnicity & Disease*. 2019;29(Suppl 1):123.

For example, OSTP, to the greatest extent possible, should seek to spread trial sites out geographically so that trials are not limited to certain geographic areas, such as urban areas. Additionally, limiting trial sites to hospitals rather than including other potential independent centers could place rural populations at a disadvantage from participating in research.

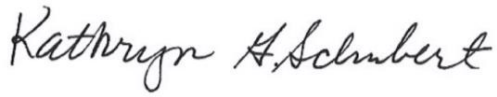
Finally, SWHR would encourage OSTP and NSC to consider how to provide incentives or financial support for individuals who enroll in emergency-related clinical trials. This support will be particularly beneficial for patients who either lack resources or support to travel for these trials.

SWHR commends OSTP for releasing this RFI to determine how to best ensure successful coordinated, large-scale clinical trials that can be activated effectively and efficiently in the event of an emergency. Time and again, we have seen the critical role that research plays in the health and well-being of our society. Prioritizing our federal research infrastructure, assessing it for weaknesses, and ensuring it has the capacity to adeptly respond to new and emerging threats is of the utmost importance.

If SWHR—or our network of peer experts—can be of assistance to OSTP and NSC as they work to build out these emergency clinical trials protocols, we stand ready to assist. Please contact me at kathryn@swhr.org or SWHR Chief Advocacy Officer Lindsey Horan at lindsey@swhr.org if you have questions or if you need additional information.

Thank you for your time and consideration.

Sincerely,



Kathryn G. Schubert, MPP
President and Chief Executive Officer
Society for Women's Health Research

The small bio-tech firm, Vaxart, located in San Francisco, California, may very well be on the cusp of revolutionizing vaccines and healthcare as we know it. Trial after trial over the years are starting to prove that Sean Tucker's science may be the answer and solution into the next generation of vaccines and healthcare. The benefits of an oral tablet vaccine against not only Covid-19 and future variants, but also against RSV, Norovirus, Influenza, possibly cancer, etc. are endless. From room temperature storage, to easier distribution, to less vaccine hesitation, the list goes on.

The concept and notion that the United States government and Big Pharma are so closely tied together in order to continue pumping out mediocre vaccines and medicines, including some that are not even needed or wanted by most people, strictly for profits, should finally be a thing of the past. Billions of dollars have already been poured into Pfizer and other Big Pharma companies since the start of the pandemic, and apparently the world is still dealing with Covid-19, as well as recent struggles with Norovirus and RSV. With the possibility of room temperature stored, easily transported and distributed, as well as easily administered oral tablets, those that may very well provide durability for up to one year, while preventing transmission, Vaxart is a company that should have been noticed, funded, and assisted in making progress long ago, especially at the beginning of the pandemic.

After years of the same old storylines with Government and Big Pharma corruption, placing profits over health and people, whether with Covid or healthcare in general, myself and many others believe it is finally time to do the right thing, properly fund Vaxart and assist them in making progress on getting their vaccines to market by any means. They may very well have one of the better, if not the best, solution to this never ending pandemic, possible future pandemics, and various other healthcare issues we face as a nation, and as a world, each year.

-Nicholas Gaudino

Comments of
The Health Record Banking Alliance
In response to
Office of Science and Technology Policy (OSTP)
Request for Information (RFI) on Clinical Research Infrastructure and Emergency Clinical Trials
87 FR 64821 (Oct. 26, 2022)
Submitted on January 25, 2023 via *emergencyclinicaltrials@ostp.eop.gov*

The Health Record Banking Alliance (HRBA)[1] offers comments in response to OSTP's Request for Information on clinical research infrastructure for purposes of conducting emergency clinical trials. *Please note: these comments complement, and should be read in conjunction with, HRBA's comments, also filed this date, in response to OSTP's Request for Information on data collection for emergency clinical trials.*

Summary of Recommendations

OSTP should implement the National Biodefense Strategy by building a clinical trial infrastructure on a foundation of Health Data Banks (HDBs) as the principal source of patient-level data. HDBs, enabled by the Interoperability Rule, will emerge as a technology-based industrial sector. HDBs will securely house patients' longitudinal health records and facilitate their use for care and for consented research. (*Please refer to the Appendix for a schematic of Health Data Banks.*)

A Health Data Bank is a secure, private- or public-sector institution. HDBs will offer secure, encrypted repository accounts that patients and other consumers own and control, and where they can aggregate, store, and analyze their health data. Health data includes (and is not limited to) encounter reports – institutional medical records – at clinician offices and hospitals, pharmaceutical data, and payment information related to health care. This information can be integrated using software at the HDB to create a longitudinal, problem-oriented Personal Health Records (PHRs), which consumers own and access to which they control.

Consumers can use their PHRs to help manage interactions with the health care system and to help understand and manage their health care. HDBs will offer analytical and advisory services to help PHR account holders interpret what is in their lifetime records. Third parties may also offer complementary analytical services. HDB PHRs will also offer patients the ability to integrate new data from various providers as time goes by in order to keep their lifetime records updated, accurate, and instantly available.

[1] The Health Record Banking Alliance, P.O. Box 6580, Falls Church, Virginia 22040, is recognized as a business league by the Internal Revenue Service under Section 501(c)(6) of the Internal Revenue Code.

Used routinely for diagnostic and other medical decisions, HDB account data can potentially improve care for all Americans, especially in underserved populations. HDBs will become part of standard care and research infrastructure in the U.S.

HDBs can be infrastructure resources for decentralized clinical trial networks. They can useful with points of care across the nation where, increasingly today, *both* clinical care and clinical research are being performed.[2] OSTP can expect HDBs, enabled by Fast Healthcare Interoperability Resources (FHIR), to provide two-way channels for communications with patients during public health emergencies at the grass roots level of U.S. health care. HDB functionality will, for example, aid rapid collection of data, including novel digital endpoints, as needed for new outbreaks. HDBs, created initially as a care resource to benefit patients and their providers, will thus also offer a permanent, standing resource for "warm-base" clinical research.

HDBs as a component of infrastructure for clinical trials are an alternative to ONC's implemention of the Trusted Exchange Framework and Common Agreement (TEFCA). This TEFCA implementation is an inherently insecure systems design. The federal government , including the Food and Drug Administration and other regulatory authorities, and the clinical trial industry cannot rely on TEFCA as a component of the National Biodefense Strategy.

Beyond its unsuitability in a secure biodefense environment, ONC's TEFCA implementation is too fragmented to be trusted for clinical trial recruitment. It is a congeries of disparate network-connecting designs assembled to preserve inefficient and soon-to-be-obsolete HIEs (Health Information Exchanges). TEFCA's standard operating procedures (SOPs) and network-centric (rather than patient-centric) architectures are not, and not required to be, uniform. Functional inefficiency is written into TEFCA's structure.

HRBA is filing a companion response to OSTP's RFI seeking input on data capture for clinical trials. There we will explain further why the current TEFCA architecture is inherently insecure, not a sufficiently reliable resource for ongoing patient care management, and all the more unfit for trial data management, where trustworthiness is paramount and flexibility to effect rapid modification of nationwide master trial protocols is likely to be a functional necessity.

We will show, in contast, how HDBs can be expected to contribute operationally in the world of clinical research as part of a robust clinical trials infrastructure.

Transformative Impact of the Cures Act and Interoperabiity Rule on Health Data Exchange

Under the Interoperability Rule, health data expressed in FHIRs ("FHIR-based health data") will be the standard for nationwide health data exchange. *Standardized* FHIR, expanded continuously under the Interoperability Rule's Standards Version Advancement Process (SVAP)[3], will enable moving patients' data from previously siloed, proprietary EHR (Electronic Health Record) systems into PHRs housed in Health Data Banks.

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[2] See: Point-of-Care Clinical Trials: Integrating Research and Care Delivery, Duke-Margolis White Paper, May 11, 2021. See also: The Coalition for Advancing Clinical Trials at Point of Care (ACT@POC).

[3] For explanation of SVAP, see Department of Health and Human Services, 21st Century Cures Act: Interoperability and Information Blocking, 85 Fed. Reg. 25642, 25644 (May 1, 2020).

As this de-siloing occurs, HDBs will replace the current health-data fax messaging system, today's de facto standard for point-to-point, health-data sharing, with *a national capability for routine, secure, convenient, point-to-point health data exchange*. This set of two-way functions includes patient-mediated digital communications and much more: point-to-point data flows between consumers and providers, providers and other providers, consumers and payors, providers and payors, payors and other payors, patients and researchers, clinical trial admininistrators and patients, clinical trial admininistrators and clinicians, clinical trial administrators and government agencies – all are benefits of standardized FHIR-based interoperability.

Parenthetically, this point-to-point functionality wholly undermines the need for a network architecture such as TEFCA to move health data for network-centric purposes.

Patient-centered health-data sharing will be bolstered by efforts such as the Centers for Medicare and Medicaid Services' proposal to establish a National Directory of Healthcare Providers & Services (NDH). The NDH would serve as a "centralized data hub" for secure healthcare provider, facility, and entity FHIR-endpoint directory information nationwide.[4] For consumers, a CMS-maintained, vetted directory of FHIR endpoints for providers and provider-related services will offer a new, essential level of trust in identifying and contacting providers reliably, securely, and directly.

The impact of such trusted functionality will produce systems benefits for enhanced health data exchange flows far beyond the directory domain itself. In form, these records will be normalized and hence "computable" to a significant degree. Patient data normalized to the degree enabled by FHIR-based standards – even at early stages of FHIR standardization – offers immediate benefits ifor research and clinical trials, whether or not conducted in emergency settings.

The initial scope of exchangeable EHR data will be limited to the current version of the USCDI (United States Core for Data Interoperability). onsumers will nevertheless have the capacity to combine basic data from copies of their EHR medical records from diverse providers into normalized, problem-oriented, longitudinal PHR health records stored in HDB accounts that they own, maintain, and control. And the scope of exchangeable data and extent of data normalization will expand each year via the Standards Version Advancement Process.

HDBs will offer analytical and advisory services to help PHR account holders interpret what is in their longitudinal records. HDB PHRs will allow patients to integrate new data from diverse providers as time goes by in order to keep their lifetime records updated, accurate, and instantly available. Third parties also will offer complementary analytical services and services to help patients involve themselves in particular research projects.

Clinician and researcher burdens due to data system complexities and lack of data normalization will be ameliorated when HDB PHR account information is readily available as a *reference* "single source of truth" for compartmentalized import into hospital and medical office EHR systems. Reliable patient data with provenance, aggregated from diverse providers,

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[4] See Centers for Medicare and Medicaid Services, Request for Information on Establishing a National Directory of Healthcare Providers & Services (NDH), Agency/Docket Number CMS-0058-NC, 87 Fed. Reg. 61018 (Oct. 7, 2022).

supplemented with contemporaneous patient observations and with data from wearables and other personal devices, will be readily searchable in problem-oriented PHRs or other enhanced formats that HDBs may adopt. This is all consistent with 45 CFR 170.215, and will support faster and safer care while reducing clinician burden.

For research purposes, patients with HDB PHR accounts will be enabled to participate voluntarily in public health initiatives such as emergency clinical trials. Consumers will have convenient means to report voluntarily to clinicians and, as appropriate, public health authorities, to seek evaluation of symptoms, advice on potential treatments or vaccinations, and research projects related to public health emergencies. These HDB PHR capabilities will complement mandatory public health reporting requirements by clinicians and other provider institutions.

These are key health care priorities for a nationwide health IT infrastructure as contemplated in section 3001(b) of the Public Health Service Act (PHSA). They illustrate *the inherently efficient, superior systems design of integrating health data around the patient*, which bestows enormous improvement in the efficiency and utility of health information exchange. That is the core systems advance that HDBs will contribute as an industrial sector to U.S. health care, the health industry, and the health research enterprise.

For all these reasons, Congress and state legislatures are likely, eventually, to consider how to encourage the private sector to invest in HDBs, and otherwise to make possible consumers' rapid, pervasive adoption of HDB PHR accounts. Tax incentives and direct subsidies for HDB accounts are among provisions to be explored.

To summarize with regard to OSTP's emergency research scenarios: PHRs housed in HDB accounts enable a patient-centered information infrastructure for medical practice and medical research. Owing to the Interoperability Rule's mandated implementation of design specifications in the Cures Act, there is no turning back from patient-centeredness.

Historical Perspective on Why Health Data Banks Have Not Emerged Earlier

Longitudinal medical records, that is, personal health records or PHRs, have long been sought; but they have proven beyond entrepreneurs' and major corporations' repeated attempts to create them. Why are they now feasible and sustainable?

History is an important guide in assessing the preconditions for the feasibility of PHRs. Google (Google Health) and Microsoft (Health Vault) failed in early, richly funded efforts to create Health Record Banks to hold Personal Health Records. Major employers, seeking to improve the health of their workforces and lower total costs of corporate health plans, also failed in consortia (for example, Dossia, Haven) to develop Health Record Bank-like systems that would offer longitudinal PHRs to their employees and their families.

These failed projects share two common characteristics. *First* was corporate recognition that workforce health costs were out of control, and belief that employee and family health across the board could be improved – and workforce health costs reduced – if employees and their families had access to, and corporate motivation to use, longitudinal Personal Health Records.

Second, none of the corporations involved in these projects could overcome data processing barriers. They had no feasible means, at scale, to extract medical records from

disparate, incompatible institutional Electronic Health Record systems in hospitals and medical offices. Every one of these projects was doomed by that constraint.

(Many excuses, such as the incompatibility of corporate cultures, were offered to explain these failures. Those factors were at best peripheral. The core cause of failure in every case was an inability to extract and exchange digital data among incompatible institutional EHR systems.)

The motivation among major corporations to reduce workforce health insurance costs and improve workers' health is as compelling now as ever. As FHIR-based, standardized digital data exchange expands to become the norm, major corporations will once again seek Health Data Bank systems. Corporate adoption of HDBs is likely to be an initial impetus for consumers employed by large corporations to aggregate their records in PHRs that their corporate employers subsidize and encourage, but that the consumer/employees themselves own and control. The same trend is likely among governments at all levels.

The Requirement for HDB Industry Regulation and Self-Regulation is Apparent Today

A proponent of HDB PHRs since 2006, HRBA is an advocate both for industry self-regulation and standards of conduct, and for federal regulation of HDBs and other private-sector repositories of consumers' health data. Federal regulation must be structured to keep bad actors from offering predatory HDB services. Regulation must also be tailored so HDBs can innovate continually in the storage, analytical, and advisory services they make available to consumers and to employers who understand the advantages of encouraging (and in many cases subsidizing) PHR use by their employees.

Government, industry, and the public will inevitably draw conclusions about privacy and other ethical factors attending the collection of medical records and other health data, and the circumstances under which that data can be communicated to whom and by whom. HRBA expects to participate in helping organize private sector development of these policies, and in helping to coordinate them with federal and state regulatory initiatives in the delivery of care, public health services, health equity, and medical research.

Conclusion

HDBs are a patient-centric technology, really a bundle of technologies, that will emerge as a significant segment of infrastructure for health care and research in the U.S. The patient-centric, integrative function of HDBs in an evolving point-to-point nationwide health information network will facilitate patient engagement on a wide scale not seen before.

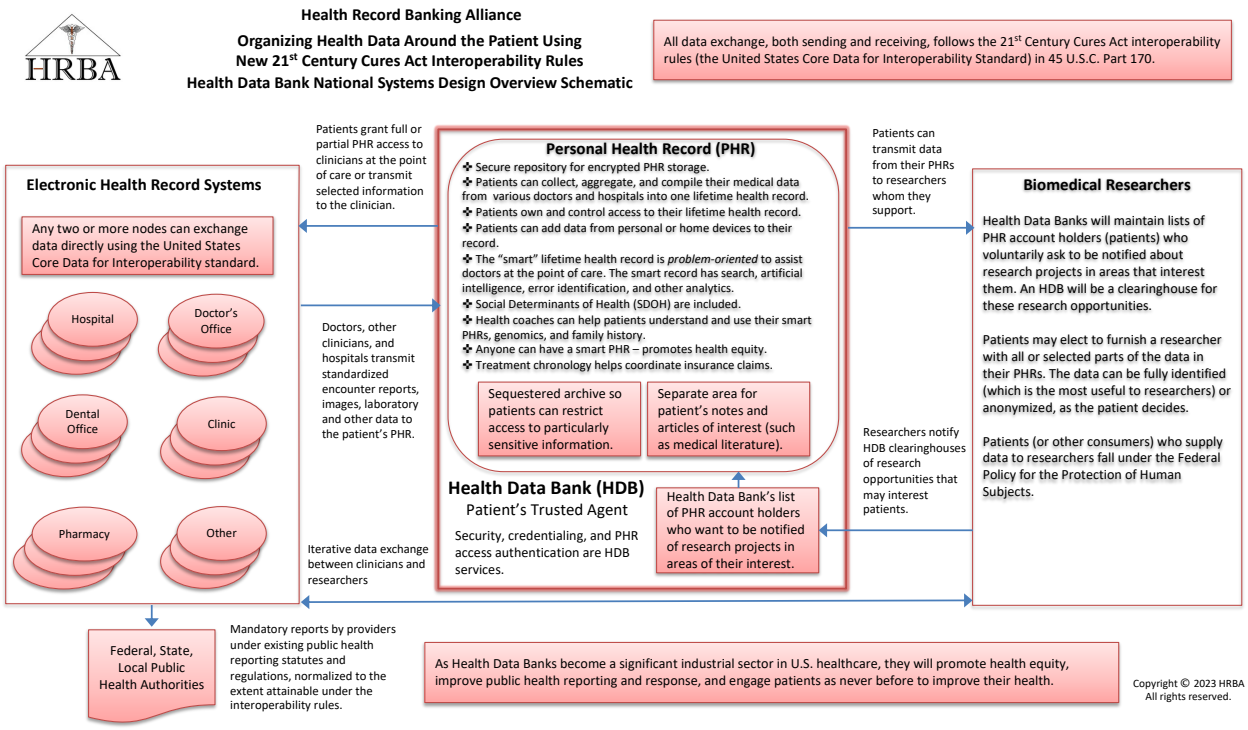
Respectfully submitted,

The Health Record Banking Alliance

/s/ Richard D. Marks
Richard D. Marks, Vice President
richardmarks@earthlink.net

Appendix

Health Data Bank (Health Record Bank) Schematic Overview
And
Descriptive Summary



Please see accompanying text on the following page.

HRBA

Health Record Banking Alliance

Organizing Health Data Around the Patient Using New 21st Century Cures Act Interoperability Rules

Health Data Bank National Systems Design Overview

A **Health Data Bank** (**HDB**, also called a Health Record Bank) is an **integrated patient information services institution**. As a **trusted agent**, it offers a **secure repository** for each individual to collect and compile their **"interoperable"** digital health information in a **smart Personal Health Record (PHR).** Individuals own and control their Personal Health Records, as in a bank checking account. With these **new information flows**, consumers will:

- exchange medical records and other health data in their Personal Health Records conveniently with doctors' offices and hospitals for better, faster care; improve patient safety; and reduce information burden on physicians by supplying an aggregated, lifetime, searchable medical record for easy and immediate reference.

- control Personal Health Record access for doctors and hospitals; family, friends, and health coaches; medical researchers; members of the press; and others as they wish.

- use their Personal Health Records to help manage their health and healthcare, and to help shop for doctors, hospitals, and health insurance.

- view their Personal Health Records on smartphones, tablets, and other computers.

Health Data Banks and Efficiency: Integrating health information around each patient via HDBs is the most efficient way to aggregate and use **"interoperable"** health data under 21st Century Cures Act regulations. It is far more efficient and useful than a collection of "apps."

HRBA's Education and Policy Advocacy: HRBA advocates government policies promoting Health Data Banks as **a major new structural sector in U.S. health care**. This systems design includes a **national regulatory framework for Health Data Banks**.

Health Data Banks and Health Equity: Health Data Banks will promote **health equity** because **everyone** can have a Personal Health Record in a Health Data Bank.

Health Data Banks as Medical Research Clearinghouses: Medical researchers cannot get enough patient data to make fast or sufficient progress. HDBs can be clearinghouses between patients and researchers. Patients can **voluntarily** list themselves with their HDBs to be informed of research projects they are interested in, and to which they want to **contribute or sell their data**. This also is a path to developing **national federated diagnostic and research databases** while respecting **patients' privacy rights** (because patients are in control). Better research will improve treatment for acute, chronic, and orphan diseases.

Health Data Banks, Security, and Patient Matching: Security, credentialing, and patient authentication and efficient matching are systems design features of HDBs.

Advanced Features of Smart Personal Health Records: Systems design features such as artificial intelligence (AI) and search capabilities, robust family history, and genomic analytics will deliver **problem-oriented data and analysis** to **mesh** with clinicians' Electronic Health Record (EHR) systems **at the point of care**. Availability of this aggregated **reference record** will reduce burdens on clinicians while improving diagnosis, treatment, and patient outcomes.

From: Ken Linsk <ken@clinicaltrials.tv>
Sent: Friday, February 3, 2023 7:59 AM
To: MBX OSTP Emergency Clinical Trials <MBX.OSTP.EmergencyClinicalTrials@ostp.eop.gov>
Subject: [EXTERNAL] Video on "Preparing U.S. Clinical Trials Infrastructure for Emergencies: A White House Virtual Roundtable"

Hello

I watched the video "Preparing U.S. Clinical Trials Infrastructure for Emergencies: A White House Virtual Roundtable" and note the part where the panel calls for more public facing approaches to clinical trials other than clinicaltrials.gov. One of those alternatives is Clinical Trials TV (>www.clinicaltrials.tv<) and another is a new start up community aimed at clinical trials (>www.clinicaltrials.m<e) that is currently being built. If you would like to know more, please respond. In the meantime, here is a summary of the video, on Clinical Trials TV:

>https://clinicaltrials.tv/video/preparing-u-s-clinical-trials-infrastructure-for-emergencies-a-white-house-virtual-roundtable/<

Thank you,
Clinical Trials TV