MEMORANDUM

September 1, 2023

To: Grail Sipes
White House Office of Science and Technology Policy (OSTP)

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Subject: Emergency Clinical Trial Data Request for Information Analysis

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On October 28, 2022, OSTP released a "Request for Information on Data Collection for Emergency Clinical Trials and Interoperability Pilot." This request for information (RFI) was originally scheduled to close on December 27, 2022 but was extended to January 27, 2023. Thirty-nine responses to the RFI were received, including one that was primarily a request for an extension to the comment period that included corporate information responsive to the RFI. STPI was asked to assist OSTP in summarizing the RFI results. This document represents that RFI summary.

Attachment: "Summary of Request for Information on Data Collection for Emergency Clinical Trials and Interoperability Pilot"

Summary of Request for Information on Data Collection for Emergency Clinical Trials and Interoperability Pilot

Brian L. Zuckerman

September 2023

Executive Summary

On October 28, 2022, OSTP released a "Request for Information on Data Collection for Emergency Clinical Trials and Interoperability Pilot." This request for information (RFI) was originally scheduled to close on December 27, 2022 but was extended to January 27, 2023. The RFI (the text of which is included as Appendix A) included 12 questions, nine of which included sub-questions or sub-parts. The RFI also asked for comments on the feasibility of an emergency clinical trials and interoperability pilot that could be conducted within 6–12 months and on the use case underlying that pilot.

Thirty-nine responses to the RFI were received and analyzed by STPI. Twenty-six of these responses came from companies, with another three provided by industry organizations. The remaining 10 responses came from academia (four responses), entities that conduct research related to clinical trials such as Federally Funded Research and Development Centers (two responses), an advocacy organization (one response), and three other clinical trials stakeholder groups.

STPI's approach to analyzing the RFI followed the RFI's structure. We began by developing a deductive coding framework corresponding to the key phrases found in the RFI questions and sub-questions. We then extracted text from the RFI responses corresponding to each question. Most responses were structured based on the questions in the RFI and so no judgement was needed to map particular blocks of text to individual questions; where responses were less well-structured STPI staff judgement was used to relate portions of the response to corresponding RFI questions and sub-questions. Once the text corresponding to each RFI question was extracted, we then mapped the text to the deductive coding framework to identify which responses were relevant to each portion of the RFI questions and to summarize relevant responses. Where the RFI responses suggested that an alternative approach might produce a more useful summary, STPI staff inductively recoded the responses to identify relevant themes for the summary. One variation from the RFI's structure is that we coded responses to Question 12 (Specific commercial capabilities) jointly with Question 11 (Pilot or demonstration project).

Key findings from the RFI analysis were:

- Most responses (26 of the 39) identified value in a pilot:
    - One response considered a pilot unnecessary because the use case has already been demonstrated.

- One response considered the technologies not likely to be developed sufficiently for a pilot to occur in the next 6–12 months.

- Of the 26 responses that identified value in a pilot, 23 suggested that their organizations already were using or were developing technologies that could be incorporated into a pilot.

- Responses were generally positive regarding the potential of the United States Core Data for Interoperability (USCDI) to support clinical research, including emergency clinical trial research. Responses noted specific positive capabilities enabled by USCDI: 1) moving trial sites toward the same data standard promotes operational efficiency, including by decreasing ambiguity in data collection across sites; 2) creating efficiencies that will become especially valuable to jump-start future emergency clinical trials; 3) establishing uniform data standards promotes interoperability generally; and 4) moving trial sites toward the same data standard promotes bulk clinical trial data export.

- None of the responses expressed concern regarding the potential value of Health Level 7 (HL7) Fast Healthcare Interoperability Resources (FHIR) application programming interfaces (APIs), but responses differed with respect to their readiness for use, with some considering them to be sufficiently developed for incorporation into a pilot and others considering them to require further development and validation.

- Responses considered Substitutable Medical Applications and Reusable Technologies (SMART) on FHIR to be promising, and several responses described already incorporating SMART on FHIR into the electronic medical record (EMR) systems that they support.

- Generally, responses identified Clinical Decision Support (CDS) Hooks as having potential for use in support of clinical research. Some responses, however, noted limitations or concerns regarding the use of CDS Hooks as clinical decision support tools, especially that this approach might be disruptive to clinician workflow or might increase clinician administrative burden or create alert fatigue.

- Responses proposed alternatives to trial complexity as the mechanism for differentiating among the appropriateness of various tools, including:

  - Studies of investigational agents (or vaccines) aimed toward regulatory approval versus observational studies or protocols examining minor modifications to the existing standard of care

  - The size of the trial and the volume of data rather than the complexity of the protocol

- Responses identified that there were approaches that could be used successfully in the context of the use case to obtain, collect, and manage consent information.

- Comments regarding the overall potential of the Trusted Exchange Framework and Common Agreement (TEFCA) were mixed. Seven responses identified potential future promise in TEFCA, especially once a research purpose has been introduced. Four responses were more concerned about TEFCA.

- Tokenization/"pseudonymization"/privacy-preserving record linkages were the most commonly discussed emerging technologies.

- Public-private partnerships, commercial demonstration projects, and agency funding were all considered useful mechanisms by which a pilot project such as the use case described in the RFI might be conducted.

Contents

1. Introduction and Summary of Responses Received

A. Introduction and Approach

On October 28, 2022, OSTP released a "Request for Information on Data Collection for Emergency Clinical Trials and Interoperability Pilot." This request for information (RFI) was originally scheduled to close on December 27, 2022 but was extended to January 27, 2023. The RFI (the text of which is included as Appendix A) included 12 questions, nine of which included sub-questions or sub-parts. The RFI also asked for comments on the feasibility of an emergency clinical trials and interoperability pilot that could be conducted within 6–12 months and on the use case underlying that pilot.

STPI's approach to analyzing the RFI followed the RFI's structure. We began by developing a deductive coding framework corresponding to the key phrases found in the RFI questions and sub-questions. We then extracted text from the RFI responses corresponding to each question. Most responses were structured based on the questions in the RFI and so no judgement was needed to map particular blocks of text to individual questions; where responses were less well-structured STPI staff judgement was used to relate portions of the response to corresponding RFI questions and sub-questions. Once the text corresponding to each RFI question was extracted, we then mapped the text to the deductive coding framework to identify which responses were relevant to each portion of the RFI questions and to summarize relevant responses. Where the RFI responses suggested that an alternative approach might produce a more useful summary, STPI staff inductively recoded the responses to identify relevant themes for the summary. One variation from the RFI's structure is that we coded responses to Question 12 (Specific commercial capabilities) jointly with Question 11 (Pilot or demonstration project), as we interpreted that organizations describing capabilities of their tools, products, and services implicitly were identifying their willingness to participate in a pilot even if they did not explicitly make such statements.

B. Overall Summary of Responses

Thirty-nine responses to the RFI were received, although one was primarily a request for an extension to the comment period that included corporate information responsive to the RFI. The list of respondents can be found in Appendix B. STPI staff characterized the organization types of those respondents (Table 1). Twenty-six of these responses came from industry, with another three provided by industry associations. The remaining 10

responses came from academia (four responses), entities that conduct research related to clinical trials such as Federally Funded Research and Development Centers (two responses), an advocacy organization (one response) and three other clinical trials stakeholder groups.

Table 1. STPI Characterization of RFI Responses by Organization Type

Organization Type	Number of Responses
Industry	26
Academia/academic research group or network	4
Stakeholder group	3
Industry association	3
Research entity	2
Advocacy organization	1

2.   Analysis of RFI Topics

In this chapter, we analyze the responses to the individual questions and topics in the RFI. The first 10 sections correspond to Questions 1–10 of the RFI, section K considers the need for a pilot and commercial capabilities (Questions 11 and 12 as well as the request to comment on the feasibility of a pilot) and the final section considers other comments, including comments on the use case steps and the assumptions underlying the pilot described in the RFI.

A.   Question 1: United States Core Data for Interoperability (USCDI)

1.   Text and Overall Summary of the Response

Question 1 of the RFI sought the following information: "*We seek input on how U.S. Government and external stakeholders might leverage USCDI and future extensions of USCDI standards (such as USCDI+, an extension that supports federal partner program specific requirements) to support emergency clinical trial research. It would also be helpful to receive comment on areas in which additional extensions might be necessary.*"

Fifteen responses were received that were germane to Question 1 and USCDI. Eleven of those responses involved companies (Castor; Datavant, Inc.; Epic; Medidata Solutions; Merative; Oracle Corporation; Palantir; Quantum Leap Healthcare Collaborative and OpenClinica, LLC; Thoughtworks; Vulcan; ZS Associates and IgniteData Ltd.), one from an academic research group or network (Vanderbilt University Medical Center/REDCap project team), one from an industry association (HIMSS Electronic Health Record Association), one from a stakeholder group (Consortium for State and Regional Interoperability) and two from research entities (MITRE, RTI International).

Twelve of the responses were positive regarding the potential of USCDI to support clinical research, including emergency clinical trial research. Some specific aspects of USCDI that responses considered to be positive or capabilities enabled by USCDI that responses mentioned were:

- Moving trial sites toward the same data standard promotes operational efficiency, including by decreasing ambiguity in data collection across sites, (RTI International, Quantum Leap, ZS Associates).

- Using USCDI to create linkages to sites' electronic medical record (EMR) systems will over time create efficiencies that will become especially valuable to jump-start future emergency clinical trials (Quantum Leap, ZS Associates).

- Establishing uniform data standards promotes interoperability generally (ZS Associates).

- Moving trial sites toward the same data standard promotes bulk clinical trial data export (ZS Associates).

Three responses (MITRE, Palantir, ZS Associates) suggested that a pilot could help to validate the use of USCDI in emergency clinical research settings. The Vanderbilt University response suggested that USCDI data elements should be made available on the National Institutes of Health's Common Data Elements repository (Vanderbilt University).

Two responses identified concerns regarding the use of USCDI for clinical research, including for emergency clinical trials. The HIMSS and Oracle responses noted that Fast Healthcare Interoperable Resources (FHIR) US Core is a more specific standard than USCDI and therefore more appropriate to ensure that it is aligned for clinical research purposes than it is to modify USCDI to support emergency clinical trials. Another concern noted is that clinical data (captured through EMRs) is intended for different purposes than clinical research data—clinical data are intended to capture the experience of individual patients to help optimize their treatment, while clinical research data are intended to capture the experience of an entire cohort of patients; developing data systems that are compliant with both EMR standards (e.g., through USCDI) and clinical research data standards (e.g., the Clinical Data Interchange Standards Consortium or CDISC standards) may be burdensome for EMR developers (Medidata).

2. USCDI Extensions

Three comments (Datavant, MITRE, Vulcan) noted that updates to USCDI to support clinical research should be a priority—once those extensions are in place they could support future emergency clinical trials as needed. Comments identified a range of potential extensions to USCDI (with varying degrees of specificity) that might be valuable:

- Add fields currently in USCDI "Comment" level status such as Adverse Events, Research Data, and Provenance (Datavant).

- Add data elements for infectious disease research (e.g., comparable to the mCODE minimal data set for oncology research and the mCARD minimal data set for cardiology) that could support future emergency clinical trials pilots (MITRE).

- Add mappings and bridging data elements to align USCDI with regulatory requirements such as the CDISC standards (Merative, Oracle).

- Add change management capabilities that allow new data elements to be incorporated as required for emergency contexts (Palantir).

- Accommodate clinical note data classes (Thoughtworks).

- Add Consent, ResearchStudy, ResearchSubject, and AdverseEvent FHIR resources (Epic, Vulcan).

B. Question 2: Health Level (HL)7 FHIR Application Programming Interfaces (APIs)

1. Text and Overall Summary of the Response

Question 2 of the RFI sought the following information: "*We seek comment on how U.S. Government and external stakeholders might leverage FHIR APIs to support research in emergency settings as well as in the pre-emergency phase, and in what areas further advances might be needed. Specific topics in this connection include:*

a. Use of an API that supports FHIR Bulk Data Access to support clinical research; whether bulk data exports from EHR systems can be used to support certain clinical trial protocols.

b. Use of the FHIR Questionnaire and Questionnaire Response resources to support clinical research."

Twenty-one responses were received that were germane to Question 2 and HL7 FHIR bulk APIs. Fifteen of those responses involved companies (Acoer; Crescendo Health; Datavant, Inc.; HealthEx; Keyrus; Medidata Solutions; Merative; Oracle Corporation; Palantir; Quantum Leap Healthcare Collaborative and OpenClinica, LLC; Thoughtworks; Vulcan; Vibrent Health; YonaLink; ZS Associates and IgniteData Ltd.), one from an academic research group or network (Vanderbilt University Medical Center/REDCap project team), two from an industry association (Healthcare Leadership Council, HIMSS Electronic Health Record Association), one from a stakeholder group (Consortium for State and Regional Interoperability), and two from research entities (MITRE, RTI International).

None of the responses expressed concern regarding the potential value of HL7 FHIR APIs, but responses differed with respect to their readiness for use. Most responses identified that these APIs had value ("FHIR US Core-based APIs are now widely deployed as part of certified HIT, while automated ingestion of FHIR Questionnaires and CQL translation into user interactions and automated data capture is starting to emerge" [HIMSS response]) or are promising for future use ("HealthEx is building a superior user experience for both PIs and patients looking to enroll and participate in trials, through the use of modern APIs available, including bulk FHIR API for accessing large population level

cohort data" [HealthEx response]). Only two responses (Keyrus, ZS Associates and IgniteData Ltd.) even mentioned "pre-emergency" situations, and neither differentiated between the pre-emergency and emergency phases with respect to API readiness. A single response (ZS Associates and IgniteData Ltd.) mentioned required advances, but the advances mentioned were organizational with respect to technology readiness rather than inherent in the development in the technology itself: "Does a hospital have the correct technology, data availability/quality, the right knowledge/skill, process and willingness to ensure that what comes out of APIs is good quality?"

Four responses referenced USCDI/Question 1 (Crescendo Health, Datavant, HIMSS, Quantum Leap). Two of them (RTI, Oracle) discussed HL7 FHIR APIs in the context of SMART on FHIR/Question 3. Other responses referenced privacy/Question 6 (MITRE), and emerging technologies/Question 10 (Palantir).

2.   Bulk Data APIs

While responses mentioned that FHIR APIs can be useful in clinical research, there was no consensus regarding the readiness of bulk data APIs for clinical use. The MITRE response considers bulk data APIs "relatively mature" and suitable for a pilot project. Several responses suggested, however, that additional development will be needed before this technology is suitable for clinical research in an emergency context:

- "There are currently limitations with how FHIR Bulk Data exports are created by EHR vendors using APIs. In Epic, patient lists must be created in the EHR before data are available to external systems through Bulk FHIR. The workflow we have created with REDCap queries data from the EHR FHIR APIs one patient at a time, but is automated and can run as a background process. This approach has been sufficient for the clinical trials we have run using the EHR FHIR integration, including those with hundreds of patients and thousands of data values. As Bulk-FHIR implementation evolves, we believe it will be possible to build additional modules and workflows that allow for faster and robust transfer" (Vanderbilt University).

- "While HL7 FHIR APIs establish a solid foundation from which to promote consistency and interoperability, they are not a complete solution to establish rigorous quality and standardization required to stand up clinical trials in an emergency" (Palantir).

- "FHIR Bulk Data Access will be essential in the transmittal of large datasets. However, FHIR Bulk Data Access isn't necessary for all use cases proposed in this RFI. As offered, it is a transactional use case (seeing patients in a clinical workflow and capturing additional supplemental data); perhaps long-term follow-up might be a use case for bulk—e.g., once patients aren't being seen for

the purposes of this trial any longer, but that's not outlined as part of this use case. Suggest deferring discussions of bulk FHIR for future consideration when a use case is better defined" (Vulcan).

- "Bulk FHIR could allow for easier data collection for chart reviews or population health studies. It can also support site feasibility and eligibility determination/recruitment, (i.e., searching through a population of patients that have a history of heart failure). Bulk FHIR adoption is not currently as broad or mature as traditional FHIR APIs" (Quantum Leap).

3. **Use of the FHIR Questionnaire and Questionnaire Response Resources to Support Clinical Research**

Responses with respect to the utility of the FHIR Questionnaire and Questionnaire Response resources to support clinical use both include examples that consider them ready for use and others that suggest that more development is required. Responses that consider these tools ready for use are:

- "FHIR-based APIs deployed for certification typically include QuestionnaireResponse as specified in FHIR US Core, even though USCDI v1, v2, or v3 do not include data using that resource. However, Questionnaire is not yet part of FHIR US Core, thus not as likely to be widely available across certified health information technology (IT)" (HIMSS).

- "The HL7 FHIR questionnaire and questionnaire response resources are appropriate mechanisms to query the data of interest" (Oracle).

- "While not every operation in DEQM may be necessary, standards such as Bulk FHIR and FHIR Questionnaire are relatively more mature and should be strongly considered for the pilot" (MITRE).

- "This can be used to support surveying recruited participants, site coordinators, and principal investigators. The data can be associated with the study being conducted and reduces latency to have timely data from a clinical trial" (Thoughtworks).

Responses that suggested that more development is required include:

- "Clinical researchers have typically used REDCap to collect questionnaire data. Attempts to push or pull data from the FHIR QuestionnaireResponse resource in Epic and Cerner are ongoing. In Epic, the workflow for feeding structured EDC data into the EHR via FHIR Questionnaire and Questionnaire responses (using recent release methods), but the dependencies and workflow are complex and project-specific. This is a good area for exploration using pilot studies which

could then inform larger scalable solutions and we would be interested in tackling this problem" (Vanderbilt).

- "The FHIR Questionnaire is a structured approach to the metadata that defines how the content is presented to a subject. Within clinical trials today, validated instruments are already widely utilized to collect quality of life as well as specialized responses – and are based on medical research. A modification of these instruments would require an industry shift as alterations to the design are typically not allowed per licensing agreements. A marrying of the two would be required to ensure ease of mapping or each questionnaire would need to be created from scratch, further delaying the start up of an emergency use clinical trial" (Merative).

- "FHIR Questionnaire and QuestionnaireResponse offer potential to reduce patient burden, by eliminating duplication for participant reported outcomes (ePROs)— if a patient portal requests a standardized instrument and a trial-specific ePRO system requires the same instrument for the patient on the trial, the EHR-based patient portal should be able to share that data. However, the limited semantic capabilities of these FHIR resources makes this difficult to do, and is an area for further development by standards organizations" (Quantum Leap).

- "On principle, the use of questionnaire and QuestionnaireResponse are flexible, highly adaptable, and extensible. There are great tools to leverage, such as LHC-Forms, to develop and implement assessments to capture patient-reported outcomes and other trial data. However, this capability lacks sophistication for clinical trial use, often requires adaptations to support the analysis side of trial work, and is only in somewhat limited use today" (RTI).

The Vulcan response ("FHIR resources already supported by certified EHRs and fit for purpose to the data classes of interest for the trial should be used. The FHIR Questionnaire resources should be reserved for data that isn't otherwise represented by the fit-for-data-class FHIR resources.") suggested that these technologies are ready for use— but may only be appropriate to use in limited circumstances.

C. Question 3: Substitutable Medical Applications and Reusable Technologies (SMART) on FHIR APIs

1. Text and Overall Summary of the Response

Question 3 of the RFI sought the following information: "*We seek input on how U.S. Government and external stakeholders might leverage SMART on FHIR APIs, and in what areas further extensions might be needed. It would be helpful to receive comments on:*

a. The most promising ways to create SMART on FHIR technologies that are portable across different institutions and EHR systems, but also provide adequate functionality to support emergency clinical trial research.

b. Whether the portability of SMART on FHIR tools provides a way to reach institutions and sites that have limited information technology resources; any promising ways to use SMART on FHIR to expand clinical research into underserved settings.

Seventeen responses were received that were germane to Question 3 and SMART on FHIR APIs. Thirteen of those responses were from companies (Castor; Epic; HealthEx; Medidata Solutions; Merative; Oracle Corporation; Palantir; Quantum Leap Healthcare Collaborative and OpenClinica, LLC; Suncoast RHIO; Thoughtworks; Vulcan; YonaLink; ZS Associates and IgniteData Ltd.), one from an academic research group or network (Vanderbilt University Medical Center/REDCap project team), one from an industry association (HIMSS Electronic Health Record Association), and two from a research entity (MITRE, RTI International).

All 17 responses considered SMART on FHIR to be a promising approach, although the MITRE response expressed a degree of caution ("MITRE recommends that SMART on FHIR applications be used considerately."). Five responses (HealthEx, MITRE, Oracle, Palantir, RTI) discussed SMART on FHIR in the context of or while referring to HL7 FHIR bulk APIs (Question 2). The Castor response discussed SMART on FHIR in concert with CDS Hooks (Question 4), while the MITRE response discussed applications of SMART on FHIR that overlap with privacy and consent (Question 6).

Several responses described already incorporating SMART on FHIR into the EMR systems that they support (e.g., companies such as Suncoast RHIP or YonaLink or the REDCap data management system described in the Vanderbilt University Medical Center response). Four of the responses discussed extensions, but those comments tended not to be technical in nature. The ZS Associates and IgniteData response noted that while several companies that sponsor clinical trials (e.g., Janssen, Bayer, Sanofi, and AstraZeneca) already use SMART applications, adding U.S. government-sponsored clinical trials could create a critical mass of users. The MITRE response described the need for research in using SMART on FHIR to facilitate the generation of a common data set such as one conformant to the Observational Medical Outcomes Partnership (OMOP) Common Data Model. The MITRE response also suggested patient-facing SMART on FHIR applications for research purposes. The Epic response suggested using Connectathons as a mechanism for demonstrating the value of the SMART on FHIR approach. The Castor response mentioned "technical and legal roadblocks" generally.

2.   Promising Approaches to Portability

Six of the responses discussed approaches to portability, although none of them specifically addressed the potential tradeoff between portability and sufficient functionality for clinical research implicit in the RFI question. Comments were:

- Employ "build-once, use many" designs to limit burdens (Vanderbilt University and RTI responses).

- Sharing patient data between different institutions and EHR systems is critical in emergency settings (Castor).

- SMART on FHIR can facilitate clinical research by writing data to multiple points at the same time (e.g., to the EHR and simultaneously to a registry) and can help to standardize the requested data elements across all organizations (Vulcan).

- SMART for FHIR can enable launch points from directly within the patient chart, providing a highly integrated way to collect research data (HealthEx).

- Mobile apps using SMART for FHIR can enable portability (Thoughtworks).

3.   Researching Underserved Institutions

Eleven of the responses discussed the potential value of SMART on FHIR in reaching institutions and sites that have limited information technology resources. The majority of those responses identified these approaches as requiring relatively limited quantities of skilled personnel time to implement—though these responses noted that institutions must still have a baseline level of IT personnel skill. Some of the responses discussed the potential value of SMART on FHIR in extending clinical research to traditionally underserved institutions. Points made were:

- SMART on FHIR allows for a "bring your own device" approach, whereby hospitals and clinics in under-resourced settings can use mobile applications and cloud-based data collection rather than requiring EMR installation before they can participate in clinical research (Merative, Thoughtworks).

- Many hospitals and clinics in rural and other under-resourced settings have installed EMR systems—SMART on FHIR allows those institutions to share data and participate in clinical research (RTI International).

- SMART on FHIR allows for the development of applications that facilitate centralized trial management and monitoring, such as to review patient information (e.g., electronic case report forms or eCRFs) remotely, to enable institutions with more limited clinical research support staff to participate in trials (Palantir).

A final point noted in the Medidata Solutions response is that there is an opportunity for the Office of the National Coordinator for Health Information Technology (ONC) to create resources to help institutions build capacity around SMART on FHIR, a quick start guide or tutorial, a Github repository with app examples, and an online testing toolset.

D. Question 4: Clinical Decision Support (CDS) Hooks

1. Text and Overall Summary of Responses

Question 4 of the RFI sought the following information: "*We seek comments on how the HL7 CDS Hooks specification might be used to support clinical research, for example by creating prompts within the practitioner workflow during interaction with patients; and any advances that might be needed to support the use case described above.*"

Fourteen responses were received that were germane to Question 4 and CDS Hooks. Ten of those responses involved companies (Castor; Epic; Medidata Solutions; Merative; Oracle Corporation; Palantir; Quantum Leap Healthcare Collaborative and OpenClinica, LLC; Thoughtworks; Vulcan; ZS Associates and IgniteData Ltd.), one from an academic research group or network (Vanderbilt University Medical Center/REDCap project team), one from an industry association (HIMSS Electronic Health Record Association), and two from research entities (MITRE, RTI International).

Generally, responses identified CDS Hooks as having potential for use in support of clinical research, with 11 of the 14 responses suggesting the approach is promising. Four responses specified that CDS Hooks were valuable in concert with SMART on FHIR applications (RFI Question 3) and one specifying that CDS Hooks were valuable in concert with HL7 Bulk APIs (RFI Question 2). Several responses, however, noted limitations or concerns regarding the use of CDS Hooks as clinical decision support tools. One response (Ignite Data) noted that CDS Hooks do not take advantage of "big data" approaches. Responses (Epic, Palantir, Vulcan) noted that this approach might be disruptive to clinician workflow or might increase clinician administrative burden or create alert fatigue, with the Palantir response recommending "non-standards based approaches for EHR-to-electronic data capture" as an alternative to CDS Hooks.

2. Advances to Support the Use Case

None of the responses identified specific technological advances that would support the use of CDS Hooks. Three responses (Vanderbilt, Quantum Leap, MITRE) noted that additional pilot efforts and infrastructure development would be valuable in helping to mature the CDS Hooks approach, with the MITRE response providing the specific example of piloting the use of CDS Hooks in the context of developing the mCODE data model for oncology, including through the ICAREdata project.

Two responses (HIMSS, Medidata Solutions) described opportunities in the context of ONC's standards development efforts. The Medidata Solutions response noted that ONC could include CDS Hooks as part of its Certified EHR Technology criteria, while the HIMSS response suggested that CDS Hooks could be incorporated into future updates to the 21st Century Cures Act Final Rule.[1]

E. Question 5: Operationalizing Protocols of Varying Complexity

1. Text and Overall Summary of Responses

Question 5 of the RFI sought the following information: *"Operationalizing protocols of varying complexity. As noted above, emergency clinical trial designs could range from relatively simple protocols to more complex studies involving the evaluation of investigational agents. We would appreciate comments on the following topics:*

a. Whether any of the tools described above might be particularly well suited for certain types of studies.

b. For example,

i. Whether a bulk FHIR API export could be used to gather data for a simple trial protocol that is relatively close to the standard of care for a particular condition.

ii. Whether a FHIR Questionnaire/ QuestionnaireResponse or a SMART on FHIR form would be useful in capturing data for a more complex protocol, such as one that involves an investigational agent.

c. Any technical limitations that we should be aware of regarding use of the above tools to operationalize clinical trial protocols."

Thirteen responses were received that were germane to Question 5 and operationalizing complexity. Eight of those responses involved companies (Epic; Medidata Solutions; Oracle Corporation; Palantir; Quantum Leap Healthcare Collaborative and OpenClinica, LLC; Vulcan; Vibrent Health; ZS Associates and IgniteData Ltd.), two from academic medical center-based research networks (NHLBI Collaborating Network of Networks for Evaluating COVID-19 and Therapeutic Strategies, Vanderbilt University Medical Center/REDCap project team), one from an industry association (HIMSS Electronic Health Record Association), and two from research entities (MITRE, RTI International).

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[1] 85 FR 25642

2.   **Suitability for Particular Types of Studies**

Responses offered several proposed alternatives to trial complexity as the mechanism for differentiating among the appropriateness of various tools. Three of the responses (Palantir, ZS Associates, MITRE) identified a difference between studies of investigational agents (or vaccines) aimed toward regulatory approval versus observational studies or protocols examining minor modifications to the existing standard of care—with the regulatory requirements associated with new drug or vaccine approvals requiring that new tools must be meet high validation standards. Two of the responses (HIMSS and Oracle) suggested that the size of the trial and the volume of data collected was an important differentiating factor rather than the complexity of the protocol.

With respect to the utility of particular tools for particular types of studies, there was no consensus across responses:

- Bulk APIs

  - Bulk APIs are useful for simpler trials/observational trials or trials close to standard of care (RTI, ZS Associates).

  - SMART on FHIR and CDS Hooks facilitate the use of bulk APIs (ZS Associates).

  - Bulk APIs are useful when datasets are large (HIMSS).

  - Bulk APIs are useful when datasets are small or data are readily available (Oracle).

  - Bulk APIs can be useful even for complex protocols (Vanderbilt).

  - Bulk APIs are generally useful (Vibrent Health).

- FHIR Questionnaires/Questionnaire Response

  - FHIR Questionnaires are useful for protocols where data requirements are simple (HIMSS).

  - FHIR Questionnaire resources should be reserved for data that isn't otherwise represented by native FHIR resources (Epic).

  - FHIR Questionnaires and Questionnaire Response are useful when datasets are small or data are readily available (Oracle).

  - FHIR Questionnaires and Questionnaire Response can be useful for complex trials (Vulcan).

Several responses expressed concerns that these tools may not be currently useful. The Medidata Solutions, Palantir, and ZS Associates responses suggested that FHIR-based Questionnaires may be an overly complicated approach or require duplication of effort for clinicians. The Medidata Solutions, Quantum Leap, and Vulcan responses suggested that

SMART on FHIR might be a useful tool for capturing data (e.g., implementing electronic case report forms). The Epic response considered bulk FHIR APIs to be unnecessary for a pilot clinical trial, though it might be useful as a mechanism for retrieving data on patients post-trial.

3. Limitations

Several responses (e.g., HIMSS, RTI) considered bulk FHIR APIs and FHIR Questionnaire/Questionnaire Response to be technologies that are still under development and whose capabilities are still emerging. Several responses (Vanderbilt University, RTI) suggested that pilots such as the OSTP-described pilot may be useful for helping to mature these technologies. Several technical limitations were identified in the responses. With respect to bulk FHIR APIs, responses (e.g., Vanderbilt University, RTI) noted that currently bulk FHIR APIs require data to be coded and mapped in exactly the same way across sites and EMR implementations, which will require the development of new tools for local context mapping and data standardization. One specific limitation identified was specific to the Epic EMR: "Questionnaire and QuestionnaireResponse Resources in Epic have historically only able to export data captured in Epic questionnaires" (Vanderbilt University).

Other responses pointed to non-technical limitations, especially with respect to regulatory issues. One response (Medidata Solutions) suggested that regulatory mandates to use these tools, as well as regulations that specify the data quality requirements associated with submitting data to the FDA in support of investigational new drug applications, will facilitate their use (NHLBI Connects).

F. Question 6: Consent, Deidentification, Return of Results

1. Text and Overall Summary of Responses

Question 6 of the RFI sought the following information: "*The use case in this RFI contemplates that data would be managed through a central repository or repositories and made available to researchers beyond a patient's home institution.*

a. In light of this, we seek comment on how the tools described above can be used to obtain, collect and/or manage any required informed consents and/or authorizations from patients or individuals in accordance with applicable regulations.

b. We also seek input on what additional capabilities would be required to deidentify or otherwise manage protected health information. It would be helpful to receive comments on which deidentification and protection approaches are sufficiently mature to support a pilot effort in the near term.

c. Ideally, patient authorization would allow clinical trial data to be used for additional research beyond the original study. We would appreciate input on how the content collected for consent and authorization as well as the interfaces with deidentification technologies should be designed to enable flexible and responsible reuse of clinical trial data.

d. We seek comment on any technical capabilities that could support return of results to study sites or participants, where appropriate.

e. We seek comment on any regulatory or ethical guidelines that are relevant to patients' consents and authorizations under the use case described in this RFI, and on ways in which technical solutions might help ensure adherence to applicable regulatory or ethical guidelines."

Twenty-one responses included discussions related to Question 6. Seventeen came from industry (Acoer; Castor; Crescendo Health; Datavant Inc.; Epic; Keyrus; Medidata Solutions; Merative; Oracle Corporation; Palantir; Privacy Analytics; Quantum Leap Healthcare Collaborative and OpenClinica, LLC; Suncoast RHIO; Thoughtworks; Vulcan; Vibrent Health; ZS Associates and IgniteData Ltd.). One response came from an industry association (HIMSS Electronic Health Record Association), one from an academic research network (Vanderbilt University Medical Center/REDCap project team), and two from research entities (MITRE, RTI International).

Overall, all of the responses identified that there were approaches that could be used successfully in the context of the use case to obtain, collect, and manage consent. Three of the responses (Keyrus, Medidata, Vanderbilt) described the value of their organization's tools specifically to manage consent. Two responses (Acoer, Suncoast RHIO) suggested that blockchain/distributed ledger technologies could be used to manage consent and the ZS Associates document noted that tools were available to manage consent in the context of a use case such as was described in the RFI but did not provide technical detail. Other responses provided additional detail regarding one or more of the sub-questions as part of Question 6.

2.   Managing Informed Consents and Authorizations

Ten of the responses were specific to the first sub-question regarding managing informed consent and authorizations. Approaches discussed were:

- Use of FHIR Consent resources (Castor, MITRE, RTI, Vulcan)—although the MITRE response considers these resources to be a subject of active investigation and testing rather considering them as ready for use

- Use of APIs generally (MITRE, Vibrent)

- Use of dynamic consent techniques (Oracle, Palantir), with the specific example of the NIH All of Us approach recommended (Oracle)

- Use of smart contracts (Thoughtworks)

The Merative response suggested that tools were available, but did not specify any particular approaches or tools. The Datavant response identified multiple commercial tools available for managing informed consent consonant with the use case, "Many eConsent platforms (e.g. Medidata, Medable, Science 37) have been developed that can consolidate the site experience of consent capture, PII management, and PPRL generation."

3. De-identification and Data Protection Approaches

Ten of the responses were specific to the second category. Most of the responses considered tools to be available currently to allow the use case to be met, although two (MITRE, RTI) suggest that the tools are still emerging or need testing to ensure that the use case described in the RFI can be met. Specific types of tools discussed with respect to de-identification were:

- Tokenization/"pseudonymization"/privacy-preserving record linkages (Crescendo Health, Epic, HIMSS, MITRE, Oracle)

- Use of FHIR APIs (Palantir, Quantum Leap, RTI)

- Statistical de-identification tools (Privacy Analytics)

- Differential privacy techniques facilitate de-identification (Palantir)

Two responses (MITRE, Thoughtworks) noted that data that conform to the OMOP Common Data Model as the data repository standard were amenable to successful de-identification.

4. Reuse of Clinical Trial Data

Six responses discussed techniques for reusing patient data. Three of these responses (e.g., Oracle, Merative, Palantir) discussed best practices for patient data reuse generally, but some discussed particular technologies or tools. RTI and HIMSS discussed the value of FHIR-based tools for facilitating reuse, including HIMSS' highlighting FHIR's Security Labeling tools and noting the San Diego LEAP project as an example; the RTI response mentioned the FHIR Consent and ResearchStudy resources. The Thoughtworks response suggested the value of the OMOP Common Data Model as the data repository standard in context of this sub-question as well as in the context of the previous sub-question.

5. Data Return to Sites and Patients

Seven responses discussed techniques for returning data to sites and patients, and all considered it feasible to make use of existing practices to accomplish this goal. Five responses (Castor, HIMSS, Palantir, RTI, Thoughtworks) discussed using FHIR-based tools to enable returning data, while the Oracle response mentioned that returning data "is well supported through cloud-enabled software" and CrescendoHealth referenced "patient-centric methods" described in its responses to the first five RFI questions.

6. Regulatory and Ethical Considerations

Four comments related to this sub-question were identified. Points made as part of these responses included:

- "Allow sites with an existing e-consenting platform to use that platform as long as it supports the FHIR Consent resources. This would ensure that information about the signed consent could be transmitted to the sponsoring entity for their records" (Castor).

- "Consumer-mediated data exchange may offer researchers a way to acquire the EHR data they need without confronting these logistical barriers. There are two approaches. In one, which we call Download and Send, study participants use a consumer-facing app to download and aggregate their own health records, which they then contribute to the research database. In the other, which we call Transmit, study participants use an app that directs their providers to transmit their data to the research database" (RTI International).

- "ONC rulemaking has made it much easier for consumers to access and use their own EHR data with the assistance of any consumer-facing apps that leverage FHIR APIs" (RTI International).

- "Integrate in the workflow for an IRB assessing research proposals and approving can be instrumented to support transparency and adherence. The other aspects can be around the handling of data submissions and approval by the principal investigator or their delegate" (Thoughtworks).

The Palantir response discussed purpose-based access controls as a way of building confidence and trust in privacy-enhancing technologies as part of the answer to Question 6. Although the response did not specifically relate trust-building to sub-question 6e, the response did mention that records of which users were granted access to which data could be made available to auditors.

G. Question 7: User Interface and User Experience

1. Text and Overall Summary of Responses

Question 7 of the RFI sought the following information: "*With all of the above technologies, we seek input on:*

a. The best way to optimize the experience of health care providers, administrators, and other users, so as to maximize the utility and uptake of the product.

b. To the extent a particular form, app or other tool requires input from a health care provider or other user, the best ways to increase the likelihood that users will actually provide that input. It would be helpful to receive comments on methods that are available for completing empty fields after the fact, or otherwise managing any missing data.

c. For clinicians and health IT users: what existing tools, apps, or processes you have found most usable and why."

Seventeen responses included discussions related to Question 7. Fourteen came from industry (Acoer; Crescendo Health; DataCubed; Epic; Keyrus; Medidata Solutions; Merative; Oracle Corporation; Palantir; Quantum Leap Healthcare Collaborative and OpenClinica, LLC; Thoughtworks; Vulcan; Vibrent Health; ZS Associates and IgniteData Ltd.). One response came from an industry association (HIMSS Electronic Health Record Association), one from an academic research network (Vanderbilt University Medical Center/REDCap project team), and one from a research entity (RTI International). Two of the industry responses (DataCubed, Keyrus) framed their answers solely in the context of the value of their firms' technologies without responding to the underlying questions and considering them in terms of lessons learned and best practices for optimizing uptake or maximizing the likelihood that users will provide the required input. The other 15 responses addressed one or more aspects of the question specifically.

2. Optimizing User Experience

Responses to this portion of the question were variable and appear to have interpreted the phrases in a variety of ways. One theme mentioned by several responses (Medidata Solutions, Merative, Oracle, Vanderbilt University, Vibrent Health) is that designers should integrate any new tool with existing EMR systems to minimize training needs and clinician burden. Other suggestions included:

- Prefill data wherever possible (Medidata Solutions)

- Simplify data collection wherever possible (Epic, Oracle)

- Simplify user experience by eliminating unnecessary actions (Oracle)

- Use API interfaces to support seamless integration (Thoughtworks)

- Design the user experience well to make users want to participate (RTI International, Vibrent Health)

- Pay close attention to how tool fits into clinician workflow (RTI International)

- Build consensus among all affected stakeholders (including researchers, clinicians, and patients) and across vendors (Vulcan)

- Involve healthcare providers in early stage discussions around new solutions (ZS Associates)

3. **Increasing the Likelihood of Providing Data and Addressing Missing Data**

As with the first sub-question, responses grappled with the issue of providing data and addressing missing data in a variety of ways. A suggestion made in several comments is to minimize the amount of data required and pre-enter data where possible, including with the assistance of APIs (CrescendoHealth, Oracle, Quantum Leap, RTI International). Other suggestions were:

- It is always possible for users who are unable to synchronize data capture across systems to fill in the information manually (HIMSS, ZA Associates)

- Give patients financial incentives to contribute their data (Acoer, CrescendoHealth)

- Use structured fields to capture data in a standardized format that preserves data quality (Oracle)

- Collect claims data as a complementary source of patient information (CrescendoHealth)

- Only incorporate "hard stops" or required data for patient safety-critical information—if clinicians are forced to fill out forms with un-needed information, data completeness may suffer (Epic)

- Verify bulk intake data on require fields and trigger notifications where missing data may lead to bias (Thoughtworks)

- Clinical protocols should not require any specific EMR user interface or clinician workflows—sites, even those using the same EMR, may benefit from customization to their specific workflow strategies (Epic)

- Streamline user training (Oracle)

- Embed quality assurance features into tools that allow supervisors to assign data capture responsibilities to study personnel, creating incentives for the front-line staff to capture complete data

4. Suggestions Regarding Highly Usable Tools and Processes

Responses to this question included both best practices-type statements similar to the information provided in response to sub-questions a) and b) of Question 7, identification of categories of tools (e.g., SMART on FHIR) discussed elsewhere in the RFI, and identification of other tools.

- Generic best practices

    – Manage missing data by trying to understand its source (Oracle)

    – Leverage existing clinical tools (RTI International)

    – Flag required actions within clinical applications to reduce barriers to use (RTI International)

    – Use Python and R coding languages, while connecting to APIs, for data science-based approaches (Thoughtworks)

- Tools mentioned in the RFI

    – SMART on FHIR applications (HIMSS, Medidata Solutions)

    – USCDI-based APIs (HIMSS, Oracle) to minimize data collection

    – FHIR Questionnaire (Oracle) to minimize data collection

    – CDS Hooks (HIMSS)

- Mention of tools besides the respondents' own systems

    – UpHealth (Acoer), which uses FHIR APIs to link patient health care records

H. Question 8: Capturing Data

1. Text and Overall Summary

Question 8 of the RFI sought the following information: "*a. We seek comment on the most promising technical approaches that would leverage common APIs to translate a particular clinical trial's data elements into data elements captured by user-facing tools (e.g., FHIR Questionnaire feeding into a SMART on FHIR form or application).*

b. If a tool such as a FHIR Questionnaire, FHIR QuestionnaireResponse, or SMART form or app is used to capture required data elements in this way, we seek comment on whether that creates an effective method for ''pushing out'' a research protocol to investigators and sites.

c. It would be helpful to receive comments on how best to ensure compliance with regulatory requirements for eCRFs when designing interfaces for data capture."

Ten of the RFI responses were relevant to question 8. Seven of those responses were from industry (Epic; Keyrus; Oracle Corporation; Quantum Leap Healthcare Collaborative and OpenClinica, LLC; Vulcan; Vibrent Health; ZS Associates and IgniteData Ltd.). One response came from an industry association (HIMSS Electronic Health Record Association), one from an academic research network (Vanderbilt University Medical Center/REDCap project team), and one from a research entity (RTI International).

2. **Promising Technical Approaches for Leveraging Common APIs for Data Capture**

There were a small number of responses that specifically discussed promising technical approaches. The HIMSS response described a workflow starting with CDS Hooks to invoke interactions with researchers, followed by sharing a FHIR Questionnaire, with an FHIR-based application or the source's health IT system ingesting the questionnaire and determining which data could be gathered automatically using US Core-based APIs or bulk data exports. The Epic, Oracle, and Quantum Leap responses discussed promising approaches for expanding direct-to-patients data capture, including the ability to push eCRFs to participants and using SMART on FHIR applications focused on providers. Notably, two responses (Epic, RTI International in addition to Vanderbilt University) mentioned Vanderbilt's REDCap as a successful example of how to provide forms making use of a SMART on FHIR application.

3. **Effectiveness of FHIR-Based Tools for Pushing Protocols to Investigators and Sites**

Responses were not positive with respect to comments on the effectiveness of FHIR-based tools. Three responses identified concerns with these approaches. Two comments identified concerns with whether the FHIR Questionnaires could be used to describe the complexity of a protocol, including its various user roles and the frequency and timing of events (Vanderbilt University, RTI International). Another expressed concerns with respect to the complexity of the tool itself and whether this approach would be scalable (ZS Associates). The HIMSS response considered tools making use of the FHIR Questionnaire to be in the early stages of development.

4. **Ensuring Regulatory Requirements Are Met when Designing Data Capture Interfaces**

Responses expressed a range of opinions regarding ensuring that regulatory requirements are met when these approaches are used. The ZS Associates response noted that EMR systems were not originally designed for clinical research, which poses challenges. The Oracle response, on the other hand, noted that their tools have been built

to be compliant with regulatory guidelines in the United States and internationally; the Epic and RTI International responses similarly noted that EMR tools meeting existing regulatory guidelines can be extended for clinical research purposes. The HIMSS response suggested that because the FHIR-based capabilities and tools are still under development, discussion of regulatory requirements is premature. The Vanderbilt response, on the other hand, suggested that validating FHIR-based approaches would be a useful pilot project—both for validating technologies such as their REDCap and for developing generalizable approaches.

I. Question 9: Trusted Exchange Framework and Common Agreement (TEFCA) and Qualified Health Information Networks (QHIN)

1. Text and Overall Summary

Question 9 of the RFI sought the following information: "*As noted above, TEFCA is in the implementation phase at this time. In the future, the TEFCA QHINs are expected to support implementation of the FHIR APIs (see the ONC Recognized Coordinating Entity's January 2022 FHIR Roadmap for TEFCA Exchange 6). We would appreciate comment on the opportunities and challenges regarding development of API implementations toward the use case described above, particularly given the current status of TEFCA and QHIN participation. Specific topics in this connection include the following:*

a. Certain policy and/or technical constraints will need to be specified for currently authorized Exchange Purposes Public Health). We seek comment on which of these constraints will also be applicable to a future research-focused Exchange Purpose.

b. Opportunities that may exist for using the initially authorized Exchange Purposes to accomplish the use case described in this RFI.

c. How the Public Health Exchange Purpose could be used to advance the goals of this RFI; what aspects of the use case described above might fall within the scope of the Public Health Exchange Purpose.

d. How a future research-focused Exchange Purpose could be structured to advance the goals of this RFI.

e. Other opportunities or constraints related to TEFCA that should be considered with regard to this RFI."

Twelve of the RFI responses were relevant to question 9. Seven of those responses were from industry (Datavant, Inc., Epic, Medidata Solutions, Oracle Corporation, Vulcan, Vibrent Health, ZS Associates and IgniteData Ltd.). Three responses came from industry associations (Health Record Banking Alliance, Healthcare Leadership Council, HIMSS Electronic Health Record Association), one from a

stakeholder group (The Sequoia Project), and one from a research entity (RTI International).

2. Technical and Policy Constraints

Comments regarding the overall potential of TEFCA were mixed. Seven responses (HIMSS, Medidata, Oracle, RTI International, The Sequoia Project, Vulcan, ZS Associates) spoke of the potential future promise of TEFCA, especially once a research purpose has been introduced. Four responses were more concerned about TEFCA. The Epic response noted that TEFCA is designed to facilitate data exchange by QHIN, not to support clinical research—and evolving to include clinical research would involve regulatory complexities. The Datavant response suggested that the TEFCA technical specifications are based on an outdated standard that is being replaced by FHIR. The response also noted that considerable pilot work would be required to determine whether TEFCA could support the needs of emergency clinical trials, and that existing networks (e.g., PCORI) would be better suited to support any pilot trials in the short term. The RTI response noted that conducting clinical research in a TEFCA environment will require interconnections between health information networks and research organizations that will require agreement on a technical standard (e.g., FHIR or the OMOP and organizational buy-in). The HRBA response considered TEFCA wholly unsuitable for clinical research and suggested that OSTP should recommend that TEFCA be restructured or abandoned.

3. Using the Existing Exchange Purposes to Meet the RFI Use Case

None of the responses explicitly supported the idea that existing Exchange Purposes would be sufficient to meet the RFI use case for emergency clinical trials. Four responses (Datavant, Epic, HRBA, Oracle) mentioned existing exchange purposes (e.g., Treatment; Individual Access Services). The Datavant, Epic, and HRBA responses suggested that those purposes are not designed to support emergency clinical trials research use cases such as those described in the RFI. The Oracle response suggested that the Individual Access Services Exchange Purpose could be explored for its suitability to support clinical research as described in the RFI use case.

4. Using the Public Health Exchange Purpose to Meet the RFI Use Case

None of the responses explicitly supported the idea that the Public Health Exchange Purpose would be sufficient to meet the RFI use case for emergency clinical trials. The Oracle response suggested that the Public Health Exchange Purpose could be explored for its suitability to support clinical research as described in the RFI use case. Three responses expressed various degrees of concern about this topic. The HIMSS response stated, "Not all emergency clinical trials can or should be considered a Public Health Purpose, as explicit patient consent is required for participation where identifiable data is to be used.

When unidentifiable or aggregated data is used, that may reduce these requirements, but raises privacy and ethical questions as to whether patients wish their data to be used in that manner beyond Treatment." The RTI response noted that the Public Health Exchange Purpose could be used to support emergency clinical trials as described in the RFI use case, but that for it to be effective, a Research Exchange Purpose would need to be defined. The Sequoia Project response categorically stated that the use case in the RFI does not fall within the Public Health Exchange Purpose and suggested that a Research Exchange Purpose would be required.

5.   **Structuring a Research Exchange Purpose to Meet the RFI Use Case**

While several responses mentioned the need for a TEFCA Research Exchange Purpose, none explicitly discussed how such a purpose should be structured. Comments considered closest to discussing "structure" were:

- The combination of the FHIR US Core, SMART Apps, as well as FHIR Questionnaire, Questionnaire, and CQL, within TEFCA's trust fabric enables the necessary scaling and flexibility to adjust, while focusing only on the relevant data. Establishing a research purpose of use standard operating procedure (SOP) is essential to determining how data collection guidance developed by the HL7 Vulcan accelerator would be adopted into the TEFCA fabric" (Oracle).

- "Ultimately, the development of a statement for a 'Research' exchange purpose should be pursued with relevant clinical trial contributors. As a minimum, this should include the U.S. Food and Drug Administration, the National Institutes of Health (NIH), members of the clinical research community, members of the EHR vendor community, and patients" (RTI International).

6.   **Other Opportunities or Constraints**

Two responses (EPIC, Vulcan) suggested that the topic of TEFCA and clinical research would merit its own separate RFI. Other suggestions of opportunities or constraints identified were:

- "The guidelines for Uses and disclosures for public health activities (45 CFR § 164.512 (b) (1) (i) and 45 CFR § 164.512 (b) (1) (iii)) may be applicable. QHINs may benefit from more specific guidance as to when these regulations are applicable to clinical trials and sponsors, allowing them to more effectively self-regulate their participants. Failure to do so may result in QHINs taking a more risk-averse regulatory interpretation and overly restrictive approach" (Medidata).

- "TEFCA SOPs should consider communication pathways between clinical trial sponsors and local (city and county) and state health departments" (Vibrent).

J. Question 10: Emerging Technologies

1. Text and Overall Summary

Question 10 of the RFI sought the following information: "*We welcome comments on any future technological developments we should anticipate. Relevant technical developments include but are not limited to differential privacy; federated machine learning; other technologies referenced in the recent OSTP RFI related to privacy-enhancing technologies (PET) (see Federal Register: Request for Information on Advancing Privacy-Enhancing Technologies); and technologies outside of the PET space. Specific topics in this area include:*

a. How future technologies might affect the use case and underlying assumptions laid out in this RFI.

b. How future technologies might change the nature of the software architecture, data architecture, or potential data collection solutions for clinical trials"

Fourteen of the RFI responses were relevant to question 10. Twelve of those responses were from industry (Acoer; Datavant, Inc.; Epic; Enveil; Keyrus; Oracle Corporation; Palantir; Quantum Leap Healthcare Collaborative and OpenClinica, LLC; Suncoast RHIO; Verily Life Sciences; Vulcan; ZS Associates and IgniteData Ltd.). One response came from an industry association (Health Record Banking Alliance), and one from a research entity (RTI International). Answers to question 10 took two forms. Some responses focused on privacy-preserving technologies and emerging technical methods for masking patient data. These responses did not specifically address how future technologies might affect the use case laid out in the RFI. Other responses focused on the development of emerging technologies with respect to clinical trials operations and management—and some of those comments did address the use case directly. As a result, rather than summarizing the answers to each sub-question, instead it made more sense to divide our analysis by the type of technology discussed.

2. Privacy-Preserving Technologies

Nine of the responses (all with industry affiliations) discussed various privacy-preserving technologies. Tokenization/"pseudonymization"/privacy-preserving record linkages were mentioned by six responses (Epic, Datavant, Oracle, Palantir, Vulcan, ZS Associates). Commenters noted that these approaches are already being used in clinical trials, including emergency clinical trials, for de-identifying data and allowing for patients' medical records to be imported into ongoing studies to supplement study data.

Blockchain/distributed ledgers were mentioned in three responses (Acoer, Suncoast RHIO, ZS Associates) as a potentially promising future technology for creating trust in records without sharing private patient information. Other technologies mentioned in one or two responses were:

- Differential privacy (Palantir, ZS Associates)

- Homomorphic encryption (Enveil, ZS Associates)

- Secure multiparty computation (Enveil)

- Decentralized machine learning approaches, including "federated" learning and "swarm" learning (Enveil, ZS Associates)

- Secured container models (Oracle)

- Synthetic data (ZS Associates)

Most of these responses focused on the promise of privacy-preserving technologies rather than concerns about them or the technological requirements of using them. The Epic response identified challenges with tokenization, in that the token-generating algorithms based on personally identifying information (e.g., address, date of birth, name) may be less successful for some subpopulations, raising the risk of being able to re-identify patients based on their unique identifiers. The ZS Associates response mentioned challenges with differential privacy, namely that the technology works less well when information is being longitudinally collected from individuals and may not work as well for certain technologies (e.g., imaging). That response also identified challenges with federated learning approaches, especially that because these approaches build models at each site rather than combining information into a single model, sites must enroll a sufficient number of patients, which may limit its utility for rare diseases or when sites enroll small numbers of patients. The ZS Associates response also notes that these technologies will require considerable computing power, a secure network architecture, and the ability to run complex cryptographic algorithms.

3. Clinical Research Technologies

Five of the responses answered Question 10 while discussing emerging clinical research approaches and technologies. The Verily response focused on the use case's assumption that electronic case report forms would be employed and suggested that the pilot consider including patient-reported data and utilizing pre-existing clinical information in EMR and other real-world data sources; incorporating these data sources would require a corresponding data architecture as part of the pilot's clinical trial infrastructure. The Quantum Leap response, while not as detailed, touched similarly on the pilot's need to incorporate multiple data streams, including patient-shared data. The HRBA response discussed the potential for health data banks and personal health records to be used in

clinical research, including to allow patients to self-identify for clinical trials, which might change the use case as described in the RFI. The RTI response mentioned that the FHIR-based tools discussed in the RFI will run using cloud services, whose privacy and security features are still being developed and matured. The Keyrus response spoke more broadly about the use of data warehousing practices and the need for flexible architectures that can accommodate emerging technologies and capabilities.

K. Questions 11 and 12: Pilot and Commercial Capabilities

1. Text and Overall Summary

Question 11 of the RFI sought the following information: "*We seek comment on how the U.S. Government can best work with external stakeholders and developers to develop a pilot or demonstration project that will operationalize clinical trial data capture and serve as a basis and model for data collection in the event of an emergency. This pilot or demonstration project could also potentially support clinical research in the pre-emergency phase. Specific topics include:*

a. Whether data can be managed through a central repository or small set of central data repositories; options for cloud-based data storage.

b. Technical options that might hold promise in the short term to enable researchers from diverse locations to analyze the data collected from multiple clinical trial sites. We also seek comment on any additional options that should be considered in the long term.

c. Whether any parts of the pilot would be appropriately supported as

i. A demonstration project with commercial partnership.

ii. A public-private partnership.

iii. An agency-funded program."

Question 12 of the RFI sought descriptions of capabilities in up to three pages of text.

Twenty-eight of the responses were coded as discussing the need for a pilot and (assuming a need was identified) capabilities that their organizations might bring to that pilot, including:

- Twenty-one industry responses (AccendoWave; Acoer; Castor; Crescendo Health; DataCubed; Datavant, Inc.; EnVeil; Epic; Faro Health; HealthEx; Keyrus; Medidata Solutions; Merative; Oracle Corporation; Palantir; Quantum Leap Healthcare Collaborative and OpenClinica, LLC; TERIDA; Vulcan; Vibrent Health; YonaLink; ZS Associates and IgniteData Ltd.)

- Two industry organizations (Healthcare Leadership Council, HIMSS Electronic Health Record Association)

- Two stakeholder groups (Consortium for State and Regional Interoperability, Scientific Knowledge Accelerator Foundation)

- Two academic research groups or networks (Vanderbilt University Medical Center/REDCap project team and an individual response)

- One research entity (RTI International)

Of these 28 responses, 26 identified value in a pilot, with the individual response considering that a pilot to be unnecessary because the use case has already been demonstrated and the Scientific Knowledge Accelerator Foundation response considered the technologies (specifically for model structured eligibility criteria) unlikely to be developed sufficiently for a pilot to occur in the next 6–12 months.

2. Company Capabilities in a Pilot

Of the 26 responses that identified value in a pilot, 23 suggested that their organizations already were using or were developing technologies that could be incorporated into a pilot. Fifteen of these (Acoer; Castor; Epic; HealthEx; Keyrus; Medidata Solutions; Merative; Oracle Corporation; Palantir; Quantum Leap Healthcare Collaborative and OpenClinica, LLC; Vanderbilt University Medical Center/REDCap project team; Vulcan; Vibrent Health; YonaLink; ZS Associates and IgniteData Ltd.) described their tools as being useful for conducting the clinical research required, including incorporating EMR data into the clinical research setting. Other companies described technologies that could be incorporated into a larger emergency trial, including:

- Two companies that develop privacy-enhancing tools that would be useful for securing patient data (Datavant, Enveil)

- Two companies describing tools for collecting data from patients (Crescendo Health, DataCubed)

- A stakeholder group focused on EMR data (Consortium for State and Regional Interoperability)

- A company focused on clinical protocol development software (Faro Health)

- A company providing secure data storage as well as privacy-protecting solutions (TERIDA)

- A company producing pain measurement technologies (AccendoWave)

The two industry associations (Healthcare Leadership Council, HIMSS Electronic Health Record Association) and the research entity (RTI International) described

capabilities valuable in a pilot generally. The RTI response identified two potential exemplars: the NIH All of Us clinical trial as an example of a trial using a central repository that meets many of the specifications of the RFI use case and the NIH Cloud Platform Interoperability Effort as an example of a federated data ecosystem.

3. Cloud Storage and Central Repositories

Eight responses (Acoer, Merative, Oracle, Palantir, RTI International, Vanderbilt, Vibrent, ZS Associates) identified that a central repository making use of cloud storage could be used for the pilot. No responses explicitly suggested that cloud storage was inappropriate or infeasible given the RFI use case. Some more detailed responses were:

- "The foundation of the pilot, and the long-term capability, should be managed through a logically shared/federated data repository (LS/FDR). A LS/FDR could operate as a shared cloud-based platform/infrastructure—providing central capabilities to researchers—while the actual data and access could be granularly configured to ensure data owners retain control and transparency over their data" (Palantir).

- "All of Us Research Program uses a central data repository to collect data from a wide variety of sources, including surveys, EHRs, biosamples, physical measurements, and wearables like the Fitbit. The OMOP Common Data Model (CDM) is used to standardize these data for researchers. After harmonizing the EHR data to meet the specifications of the OMOP CDM, the data are processed to ensure participant privacy is protected" (RTI International).

- "For pilot work specific to central/site data collection and transfer, we would envision setting up a REDCap instance in the cloud (AWS, GCP, or Azure) as a central repository. Existing REDCap tools could be used to automate data transfer from contributing sites' REDCap instance to the central repository instance used to harmonize all data" (Vanderbilt).

4. Analyzing Data from Multiple Clinical Trial Sites

Four responses (Acoer, Merative, RTI, Vanderbilt) explicitly addressed Question 11b regarding analyzing data from multiple clinical trial sites. These comments all identified approaches for conducting analyses, but they tended not to be specific (e.g., Acoer's response noted the use of blockchain, and the Merative and Vanderbilt responses noted that their tools are capable of meeting the RFI use case). The RTI response identified companies (e.g., Evidentli's Piano platform, Smile Digital Health's FHIR efforts) with notable technology development efforts to address components of the RFI use case.

5. Partnerships

Eight responses discussed potential partnership mechanisms that might be valuable in a pilot effort. The Acoer, Castor, Keyrus, Medidata, and Merative responses were open to commercial demonstration pilots (although the Acoer response did not consider this the optimal approach). The Acoer, HIMSS, HLC, Keyrus, Medidata, and Palantir responses considered a public-private partnership (PPP) to be the best approach (with the Acoer response favoring a PPP over other solutions). The Acoer, Castor, Keyrus, and Medidata responses considered an agency-sponsored effort to be a useful approach. Only the Castor response did mention a PPP as a meritorious approach, while the two industry associations (HLC, HIMSS) and the Acoer and Palantir corporate responses considered a PPP the best option.

L. Other Comments on the RFI Use Case

1. Text and Overall Summary

The RFI described a seven-stage use case for an emergency clinical trial pilot:

1. A U.S.-level governing entity would oversee development of a clinical trial protocol for broad distribution across clinical trial networks and sites.

2. Study sites would enroll participants in the trial (potentially using software mechanisms that can alert sites to potential subjects for a specific protocol in a manner that increases the diversity of trial populations). Sites would obtain appropriate e-consents and authorizations from participants.

3. Clinical trial data is typically sent to the trial sponsor though an electronic case report form (eCRF), which is the record of data that is required under the protocol to be captured for each trial participant. A data element in an eCRF is the smallest unit of observation for a particular subject.

4. The eCRFs would be transmitted electronically via common APIs to the sponsor.

5. The study site's health IT system would present the eCRF content to clinicians in a manner that expedites data collection and (ideally) fits within clinician workflows.

6. As the clinician obtains data elements to complete the eCRF, that data would be captured in the patient's electronic health record.

7. The clinical trial data would also be sent to a central data repository or small set of data repositories for researchers to analyze. It would be sent via common APIs so that researchers can easily interpret the eCRF data elements. Commercial cloud solutions are likely to house the data repository or repositories. Nonetheless, we would like a solution that would work across multiple cloud vendors.

The RFI asked for comment on the feasibility of all steps in this use case. Nine responses discussed one or more steps of the use case, including three responses from industry (Verily Life Sciences, Vulcan, YonaLink), two responses from academia (Infectious Diseases Clinical Research Consortium and an individual response), one response from a stakeholder group (Scientific Knowledge Accelerator Foundation), one response from a research entity (MITRE Corporation), one response from an advocacy organization (Good Science Project), and one response from an industry association (Health Record Banking Alliance). No responses mentioned all steps of the use case. Responses included mentions of specific use case steps and comments on them as well as more fundamental discussions of the use case and how an emergency clinical trial could be conducted in the context of the U.S. clinical trial infrastructure.

2. Specific Comments on Individual Use Case Steps

Three (Verily, YonaLink, and the individual response) responses focused on the electronic case reporting steps. All three noted that the use case assumes the electronic case reporting form will be the locus for collecting research data, with the clinician inputting data into the form. The Verily and individual responses suggested that with greater use of real-world data and direct linkages from EMR systems to the clinical research infrastructure the eCRF could become one source of data. The Verily response implied modifying step 4 so that data are not exclusively collected through the eCRF, while the individual responses directly stated that steps 4–6 should be dramatically modified or eliminated. The YonaLink response to step 4 was more technical and stated, "Rather than send the eCRFs via common APIs, we believe it would be more effective to have the eCRFs available in the same digital system that will transfer the data to the EDC." In a final mention of a specific step, the Scientific Knowledge Accelerator Foundation response noted that their entire response is germane to use case step 2: "This RFI response is specific to step 2 of the desired use case: 'Study sites would enroll participants in the trial (potentially using software mechanisms that can alert sites to potential subjects for a specific protocol in a manner that increases the diversity of trial populations). Sites would obtain appropriate e-consents and authorizations from participants.' Specifically, this RFI response describes how trial eligibility criteria structured in FHIR EvidenceVariable Resources could facilitate this step for a rapid interoperability pilot."

3. Broader Comments on the Use Case

Three comments noted that the technologies discussed in their responses could fundamentally change the nature of clinical trial conduct. Two comments (HRBA and the individual response) pointed to the future expansion of heath data banks/health data warehouses and suggested that these stores of patient data could become a valuable source of information for clinical trials, with the HRBA response suggesting that HDBs could dramatically change how clinical trials are performed: "HDBs offer secure patient-centered

data repositories and exchange infrastructure that can be shared reliably by medical practitioners and medical researchers. This is unprecedented. It eliminates costs and efforts that would arise from assuming that the clinical research enterprise and the health care delivery system will remain fundamentally separate domains as they have been for the past 60 years." The Vulcan response suggested that FHIR could dramatically change the Nation's clinical trial infrastructure: "There's an opportunity to shift from a typical to a more modernized methodology to collect and exchange clinical trial data. This reconceptualization involves using FHIR as the backbone of the collected clinical trial data, which is highly reusable, standardized, semantically decipherable, and adapted for human and machine applications."

The Good Science Project and MITRE comments raised a different point. They noted that a more effective, more modernized clinical trial infrastructure would be available for emergency clinical trials when necessary. Finally, the IDCRC response pointed to the success of Operation Warp Speed and the conduct of rapid, large, highly impactful clinical trials in support of vaccine development and suggested that the current U.S. governance structure for emergency clinical trials is effective (although it could be made more efficient).

Appendix A.
RFI Text

AGENCY: Office of Science and Technology Policy (OSTP).

ACTION: Notice of Request for Information (RFI) on Data Collection for Emergency Clinical Trials and Interoperability Pilot.

SUMMARY:

As described in the recent RFI on Clinical Research Infrastructure and Emergency Clinical Trials, 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 as needed to address outbreaks of disease and other emergencies. In this RFI on Data Collection for Emergency Clinical Trials and Interoperability Pilot, issued in partnership with the Office of the National Coordinator for Health Information Technology (ONC), OSTP and ONC seek input on viable technical strategies to distribute clinical trial protocols and capture clinical trial data using common application programming interfaces (APIs), in the pre-emergency phase as well as in emergency settings. One specific objective for this RFI is to gather information about whether there is value in a pilot or demonstration project to operationalize data capture in the near term, for example within 6-12 months of the close of comments on this RFI.

DATES: Interested persons and organizations are invited to submit comments on or before 5:00 p.m. ET on December 27, 2022.

ADDRESSES: Interested individuals and organizations should submit comments electronically to *datacollectionforclinicaltrials@ostp.eop.gov* and include "Data Collection for 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 10 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 health information technology (health IT) companies, app developers, clinical trial designers, and users of health IT products. *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 *datacollectionforclinicaltrials@ostp.eop.gov.*

SUPPLEMENTARY INFORMATION:

Background on emergency clinical trial research: OSTP (in partnership with the NSC and other Executive Office of the President components) is leading an initiative to enhance U.S. capacity to carry out clinical trials in emergency situations. This initiative is undertaken in accordance with the 2022 National Biodefense Strategy for Countering Biological Threats, Enhancing Pandemic Preparedness, and Achieving Global Health Security and aligns with the goals of the American Pandemic Preparedness Plan (AP3).

In the recent RFI on Clinical Research Infrastructure and Emergency Clinical Trials, OSTP is seeking input on the emergency clinical trials effort generally, including U.S.-level governance models to support the emergency clinical trials effort. Governance functions might include determining when coordinated, large-scale clinical research is needed, including research on countermeasures, to address outbreaks of disease or other biological incidents. A further governance function might be to develop clinical trial protocols (in coordination with external stakeholders), which could range from relatively simple studies to more complex ones involving the evaluation of investigational agents. OSTP also seeks comment in the RFI on Emergency Clinical Trials on how emergency clinical trial data should be managed to facilitate researchers' access and analysis of results. One potential model would be the use of a centralized data repository and biorepository for specimens collected during trials.

In this RFI on Data Collection for Emergency Clinical Trials and Interoperability Pilot, to further prepare the U.S. clinical trials enterprise to carry out coordinated, potentially large-scale research protocols in an emergency setting, OSTP is seeking input on how best to operationalize protocol distribution and data capture from a technical perspective. Specifically, in this RFI we seek input on viable technical strategies to distribute clinical trial protocols and capture clinical trial data using common Health Level 7 (HL7) Fast Healthcare Interoperability Resources (FHIR®)-based APIs, in the pre-emergency phase as well as in an emergency setting. We seek comment on how to build towards both of these goals in a data capture pilot or demonstration project. This pilot, if implemented, could provide training for sites in underserved communities, thereby enlarging and strengthening the overall clinical trials infrastructure.

Desired use case: OSTP is still in the process of collecting information on governance models and other aspects of the emergency clinical trials initiative. For purposes of responding to this RFI, however, we would like responders to consider the following multi-step use case.

1. A U.S.-level governing entity would oversee development of a clinical trial protocol for broad distribution across clinical trial networks and sites.

2. Study sites would enroll participants in the trial (potentially using software mechanisms that can alert sites to potential subjects for a specific protocol in a manner that increases the diversity of trial populations). Sites would obtain appropriate e-consents and authorizations from participants.

3. Clinical trial data is typically sent to the trial sponsor though an electronic case report form (eCRF), which is the record of data that is required under the protocol to be captured for each trial participant. A data element in an eCRF is the smallest unit of observation for a particular subject.

4. The eCRFs would be transmitted electronically via common APIs to the sponsor.

5. The study site's health IT system would present the eCRF content to clinicians in a manner that expedites data collection and (ideally) fits within clinician workflows.

6. As the clinician obtains data elements to complete the eCRF, that data would be captured in the patient's electronic health record.

7. The clinical trial data would also be sent to a central data repository or small set of data repositories for researchers to analyze. It would be sent via common APIs so that researchers can easily interpret the eCRF data elements. Commercial cloud solutions are likely to house the data repository or repositories. Nonetheless, we would like a solution that would work across multiple cloud vendors.

For the purposes of this RFI, we are interested in the feasibility of all steps in the above hypothetical use case; we would also like input on how much of the use case could be

operationalized in a pilot or demonstration project that might move forward in a timeframe of 6-12 months from the close of comments on this RFI.

ONC standards for interoperability: We believe that a pilot or demonstration project such as described above would be well supported by the regulatory and governance structure for interoperability of electronic health records (EHRs) that has been put in place by the Office of the National Coordinator for Health Information Technology (ONC). Among other initiatives, ONC is currently supporting development of the United States Core Data for Interoperability (USCDI) standard; the FHIR application programming interfaces (APIs); and Substitutable Medical Applications and Reusable Technologies (SMART) platform technologies that are compatible with FHIR interfaces and have given rise to a category of "SMART on FHIR" APIs. Certified health IT developers seeking certification on their Health IT Modules are currently working to meet various ONC certification criteria intended to improve data interoperability. For example, certified developers are required to implement certified API technology capable of patient and population services based on FHIR Release 4, the FHIR US Core Implementation Guide, and based on the HL7 FHIR® Bulk Data Access (Flat FHIR®) (v1.0.0: STU 1), August 22, 2019 Implementation Guide, by December 31, 2022.

In addition, ONC published the Trusted Exchange Framework, Common Agreement—Version 1, and QHIN Technical Framework—Version 1 on January 19, 2022. The overall goal of the Trusted Exchange Framework and Common Agreement (TEFCA) is to establish a universal floor for interoperability across the country. The Common Agreement will establish the infrastructure model and governing approach for users in different networks to securely share basic clinical information with each other—all under commonly agreed-to expectations and rules, and regardless of which network they happen to be in. Entities seeking to be designated as Qualified Health Information Networks (QHINs), per the Common Agreement, can apply for that designation on a voluntary basis. A QHIN is a network of organizations that work together to share health information. The goal of TEFCA is for QHINs to connect directly to each other to ensure interoperability between the networks they represent and to serve a wide range of end users.

The Common Agreement defines Exchange Purpose(s) as "the reason, as authorized by this Common Agreement including the Exchange Purposes SOP, for a Request, Use, Disclosure, or Response transmitted via QHIN-to-QHIN exchange as one step in the transmission." Although research is not an authorized Exchange Purpose under the current version of the Common Agreement, it is a planned future Exchange Purpose, and responses to this RFI could inform how TEFCA might best support research in the future.

The implementation SOPs for Public Health and some other current Exchange Purposes, including Payment, Health Care Operations, and Government Benefits Determination, have not yet been developed. These SOPs will need to specify constraints, and at least some of the to-be-defined constraints are likely to be applicable to a future research-focused Exchange Purpose. Therefore, this RFI also seeks input on how TEFCA's Public

Health Exchange Purpose Implementation SOP might be designed to enable public health authorities to answer questions that align with the activities described in this RFI.

More information on ONC data interoperability initiatives is available at *https://www.healthIT.gov,* and more specific information about TEFCA at *https://www.healthit.gov/TEFCA* and *https://rce.sequoiaproject.org/.*

Information Requested: OSTP invites input from all interested parties as outlined in the instructions. Respondents may provide information for *one or as many topics* below as they choose.

Our goal for this RFI is to support optimized data collection for clinical trials carried out across a range of institutions and sites, both in emergency settings and in the pre-emergency phase, under the use case described above. We also seek input specifically on the value of designing a pilot or demonstration project to operationalize data capture in the near term, for example within 6-12 months of the close of comments on this RFI. With those goals in mind, we request input on the following topics:

1. United States Core Data for Interoperability (USCDI). We seek input on how U.S. Government and external stakeholders might leverage USCDI and future extensions of USCDI standards (such as USCDI+, an extension that supports federal partner program-specific requirements) to support emergency clinical trial research. It would also be helpful to receive comment on areas in which additional extensions might be necessary.

2. HL7 FHIR APIs. We seek comment on how U.S. Government and external stakeholders might leverage FHIR APIs to support research in emergency settings as well as in the pre-emergency phase, and in what areas further advances might be needed. Specific topics in this connection include:

a. Use of an API that supports FHIR Bulk Data Access to support clinical research; whether bulk data exports from EHR systems can be used to support certain clinical trial protocols.

b. Use of the FHIR Questionnaire and QuestionnaireResponse resources to support clinical research.

3. SMART on FHIR APIs: We seek input on how U.S. Government and external stakeholders might leverage SMART on FHIR APIs, and in what areas further extensions might be needed. It would be helpful to receive comments on:

a. The most promising ways to create SMART on FHIR technologies that are portable across different institutions and EHR systems, but also provide adequate functionality to support emergency clinical trial research.

b. Whether the portability of SMART on FHIR tools provides a way to reach institutions and sites that have limited information technology resources; any promising ways to use SMART on FHIR to expand clinical research into underserved settings.

4. Clinical Decision Support (CDS) Hooks: We seek comments on how the HL7 CDS Hooks specification might be used to support clinical research, for example by creating prompts within the practitioner workflow during interaction with patients; and any advances that might be needed to support the use case described above.

5. Operationalizing protocols of varying complexity. As noted above, emergency clinical trial designs could range from relatively simple protocols to more complex studies involving the evaluation of investigational agents. We would appreciate comments on the following topics:

a. Whether any of the tools described above might be particularly well suited for certain types of studies.

b. For example,

i. Whether a bulk FHIR API export could be used to gather data for a simple trial protocol that is relatively close to the standard of care for a particular condition.

ii. Whether a FHIR Questionnaire/QuestionnaireResponse or a SMART on FHIR form would be useful in capturing data for a more complex protocol, such as one that involves an investigational agent.

c. Any technical limitations that we should be aware of regarding use of the above tools to operationalize clinical trial protocols.

6. Consent, deidentification, return of results. The use case in this RFI contemplates that data would be managed through a central repository or repositories and made available to researchers beyond a patient's home institution.

a. In light of this, we seek comment on how the tools described above can be used to obtain, collect and/or manage any required informed consents and/or authorizations from patients or individuals in accordance with applicable regulations.

b. We also seek input on what additional capabilities would be required to deidentify or otherwise manage protected health information. It would be helpful to receive comments on which deidentification and protection approaches are sufficiently mature to support a pilot effort in the near term.

c. Ideally, patient authorization would allow clinical trial data to be used for additional research beyond the original study. We would appreciate input on how the content collected for consent and authorization as well as the interfaces with deidentification

technologies should be designed to enable flexible and responsible reuse of clinical trial data.

d. We seek comment on any technical capabilities that could support return of results to study sites or participants, where appropriate.

e. We seek comment on any regulatory or ethical guidelines that are relevant to patients' consents and authorizations under the use case described in this RFI, and on ways in which technical solutions might help ensure adherence to applicable regulatory or ethical guidelines.

7. *User interface and experience.* With all of the above technologies, we seek input on:

a. The best way to optimize the experience of health care providers, administrators, and other users, so as to maximize the utility and uptake of the product.

b. To the extent a particular form, app or other tool requires input from a health care provider or other user, the best ways to increase the likelihood that users will actually provide that input. It would be helpful to receive comments on methods that are available for completing empty fields after the fact, or otherwise managing any missing data.

c. For clinicians and health IT users: what existing tools, apps, or processes you have found most usable and why.

8. *Capturing data elements required for clinical trial protocols.*

a. We seek comment on the most promising technical approaches that would leverage common APIs to translate a particular clinical trial's data elements into data elements captured by user-facing tools (*e.g.,* FHIR Questionnaire feeding into a SMART on FHIR form or application).

b. If a tool such as a FHIR Questionnaire, FHIR QuestionnaireResponse, or SMART form or app is used to capture required data elements in this way, we seek comment on whether that creates an effective method for "pushing out" a research protocol to investigators and sites.

c. It would be helpful to receive comments on how best to ensure compliance with regulatory requirements for eCRFs when designing interfaces for data capture.

9. *TEFCA and QHINs.* As noted above, TEFCA is in the implementation phase at this time. In the future, the TEFCA QHINs are expected to support implementation of the FHIR APIs (see the ONC Recognized Coordinating Entity's January 2022 FHIR Roadmap for TEFCA Exchange). We would appreciate comment on the opportunities and challenges regarding development of API implementations toward the use case described above, particularly given the current status of TEFCA and QHIN participation. Specific topics in this connection include the following:

a. Certain policy and/or technical constraints will need to be specified for currently authorized Exchange Purposes under the Common Agreement (*e.g.,* Public Health). We seek comment on which of these constraints will also be applicable to a future research-focused Exchange Purpose.

b. Opportunities that may exist for using the initially authorized Exchange Purposes to accomplish the use case described in this RFI.

c. How the Public Health Exchange Purpose could be used to advance the goals of this RFI; what aspects of the use case described above might fall within the scope of the Public Health Exchange Purpose.

d. How a future research-focused Exchange Purpose could be structured to advance the goals of this RFI.

e. Other opportunities or constraints related to TEFCA that should be considered with regard to this RFI.

10. Emerging technologies. We welcome comments on any future technological developments we should anticipate. Relevant technical developments include but are not limited to differential privacy; federated machine learning; other technologies referenced in the recent OSTP RFI related to privacy-enhancing technologies (PET) (*see* Federal Register**:** Request for Information on Advancing Privacy-Enhancing Technologies); and technologies outside of the PET space. Specific topics in this area include:

a. How future technologies might affect the use case and underlying assumptions laid out in this RFI.

b. How future technologies might change the nature of the software architecture, data architecture, or potential data collection solutions for clinical trials.

11. Pilot or demonstration project. We seek comment on how the U.S. Government can best work with external stakeholders and developers to develop a pilot or demonstration project that will operationalize clinical trial data capture and serve as a basis and model for data collection in the event of an emergency. This pilot or demonstration project could also potentially support clinical research in the pre-emergency phase. Specific topics include:

a. Whether data can be managed through a central repository or small set of central data repositories; options for cloud-based data storage.

b. Technical options that might hold promise in the short term to enable researchers from diverse locations to analyze the data collected from multiple clinical trial sites. We also seek comment on any additional options that should be considered in the long term.

c. Whether any parts of the pilot would be appropriately supported as

i. A demonstration project with commercial partnership.

ii. A public-private partnership.

iii. An agency-funded program.

12. Specific commercial capabilities. Commenters who are developing a technology or product that might be relevant to any of the topics set forth above are welcome to include a description of that product. Comments about a specific technology or product should be limited to three pages or less.

Dated: October 25, 2022.

Stacy Murphy,

Operations Manager.

 [FR Doc. 2022-23489 Filed 10-27-22; 8:45 am]

BILLING CODE 3270-F1-P

Appendix B.
List of Respondents, By Organization Type

- Industry
  - AccendoWave
  - Acoer
  - Castor
  - Crescendo Health
  - DataCubed
  - Datavant, Inc.
  - EnVeil
  - Epic
  - Faro Health
  - HealthEx
  - Keyrus
  - Medidata Solutions
  - Merative
  - Oracle Corporation
  - Palantir
  - Privacy Analytics
  - Quantum Leap Healthcare Collaborative and OpenClinica, LLC
  - Suncoast RHIO
  - TERIDA
  - Thoughtworks
  - TransCelerate BioPharma Inc.
  - Verily Life Sciences
  - Vulcan HL7 FHIR Accelerator

- – Vibrent Health

- – YonaLink

- – ZS Associates and IgniteData Ltd.

- Academia/academic research group or network

  - – Individual response

  - – Infectious Diseases Clinical Research Consortium

  - – NHLBI Collaborating Network of Networks for Evaluating COVID-19 and Therapeutic Strategies

  - – Vanderbilt University Medical Center/REDCap project team

- Stakeholder group

  - – Consortium for State and Regional Interoperability

  - – Scientific Knowledge Accelerator Foundation

  - – The Sequoia Project

- Industry Association

  - – Health Record Banking Alliance (HRBA)

  - – Healthcare Leadership Council

  - – HIMSS Electronic Health Record Association

- Research Entity

  - – MITRE Corporation

  - – RTI International

- Advocacy organization

  - – Good Science Project

Abbreviations

API	application programming interface
CDS	Clinical Decision Support
CDISC	Clinical Data Interchange Standards Consortium
CRF	case report form
EMR	electronic medical record
FHIR	Fast Healthcare Interoperable Resources
HL7	Health Level 7
IDA	Institute for Defense Analyses
IT	information technology
OMOP	Observational Medical Outcomes Partnership
ONC	Office of the National Coordinator for Health Information Technology
OSTP	Office of Science and Technology Policy
PPP	public-private partnership
QHIN	Qualified Health Information Network
RFI	request for information
SMART	Substitutable Medical Applications and Reusable Technologies
STPI	Science and Technology Policy Institute
TEFCA	Trusted Exchange Framework and Common Agreement
USCDI	United States Core Data for Interoperability