MITRE's Response to the OSTP RFI on Clinical Research Infrastructure and Emergency Clinical Trials

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About MITRE

MITRE is a not-for-profit company that works in the public interest to tackle difficult problems that challenge the safety, stability, security, and well-being of our nation. We operate multiple federally funded research and development centers (FFRDCs), participate in public-private partnerships across national security and civilian agency missions, and maintain an independent technology research program in areas such as artificial intelligence, intuitive data science, quantum information science, health informatics, policy and economic expertise, trustworthy autonomy, cyber threat sharing, and cyber resilience. MITRE's 10,000-plus employees work in the public interest to solve problems for a safer world, with scientific integrity being fundamental to our existence. We are prohibited from lobbying, do not develop or sell products, have no owners or shareholders, and do not compete with industry. Our multidisciplinary teams (including engineers, scientists, data analysts, organizational change specialists, policy professionals, and more) are thus free to dig into problems from all angles, with no political or commercial pressures to influence our decision-making, technical findings, or policy recommendations.

MITRE has multiple experiences relevant to the clinical trials infrastructure objectives stated in the RFI, such as those listed below:

- Established and co-leads the Coalition for Advancing Clinical Trials at the Point of Care (ACT@POC), which brings together health systems, community-based care organizations, health research organizations, and other collaborators to build an adaptable and responsive clinical trials network focused on increasing participation, improving patient access, and facilitating development of targeted therapies with important impact on patient outcomes.[1]
- Established and co-chaired the COVID-19 Healthcare Coalition (C19HCC), a private-sector led response that brought together healthcare organizations, technology firms, nonprofits, academia, and startups to preserve the healthcare delivery system and help protect U.S. populations.[2] The Coalition built rapid clinical studies based on common data models and collection techniques. Through these efforts, the coalition was able to answer key clinical questions quickly and effectively on the use of targeted therapeutics in the early days of the pandemic.
- Explored and demonstrated results for use cases under CodeX.[3]
    - The *Integrated Trial Matching for Cancer Patients and Providers* use case is exploring how to make cancer clinical trial screening more equitable and easier for all patients and providers.[4]

[1] Advancing Clinical Trials at the Point of Care. 2023. MITRE, https://actpoc.org/. Last accessed January 18, 2023

[2] COVID-19 Healthcare Coalition. 2022. MITRE, https://c19hcc.org/#. Last accessed January 18, 2023.

[3] CodeX Home. 2023. CodeX, https://confluence.hl7.org/display/COD/CodeX+Home. Last accessed January 18, 2023.

[4] Integrated Trial Matching for Cancer Patients and Providers. 2022. CodeX, https://confluence.hl7.org/display/COD/Integrated+Trial+Matching+for+Cancer+Patients+and+Providers. Last accessed January 18, 2023.

- The *Integrating Clinical Trials and Real-World Endpoints* use case is demonstrating that electronic healthcare records (EHRs) can provide high-quality clinical trial data in a way that is both more efficient and less burdensome than the current system of using separate and expensive curation processes.[5]

Introduction and Overarching Recommendations

MITRE's recommendation for emergency clinical trials is a system for routine clinical trials that is regularly exercised, routinely improved upon, and available for emergency use when needed. Such a network would ideally have several features, which we discuss in our response to the adjacent "data" RFI.

Implementing such an approach will be complicated as the healthcare system is fragmented, and the policies, governance, oversight, and leadership are siloed across multiple federal agencies, resulting in challenges in rapid, efficient, evidence-based implementation of emerging research and preparedness for emergency clinical trials. Interagency collaboration is necessary to accomplish the collaborative networks and infrastructure investments to safeguard our healthcare system for the future. Our observations and responses focus on the following key themes:

1) Collaboration and coordination across multiple public agencies and private entities is needed to create a holistic strategy to map efforts so that duplications and gaps can be identified and addressed.
2) Community representation and participation in co-designing the emergency clinical trial research infrastructure, pilots and practice runs is essential to simplify and streamline data pipelines and requirements and foster trust with vulnerable and under-resourced communities.
3) Warm base research network that offers centralized and federated models that can be utilized for clinical research and extensible to pandemic/emergency response.

Responses to Questions Posed in the RFI

1. Governance for emergency clinical trials response

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

The first step in determining an effective governance structure for this activity is to recognize that it will predominantly be a voluntary collaboration spanning a wide range of entities, each with varying levels of commitment and resources. Participants must not only feel sufficient value to warrant their continued participation but also that they have some input or influence over decisions made. That said, there must also be a strong leadership and coordination function to succeed.

[5] EHR Endpoints for Cancer Clinical Trials. 2022. CodeX, https://confluence.hl7.org/display/COD/Integrated+Trial+Matching+for+Cancer+Patients+and+Providers. Last accessed January 18, 2023.

MITRE and the Office of Management and Budget (OMB) previously encountered such a juxtaposition when designing the operating model of OMB's proposed *Government Effectiveness Advanced Research* Center. After reviewing multiple options, we settled on an approach that would also be effective in this context. This design had three components:

- A **federal government role** to leverage resources, data, and the varied opportunities for piloting ideas that are distributed throughout the government.
- A **private sector network of networks** to bring together and leverage private sector expertise and resources from throughout industry, academia, research organizations, and non-profits (and in this case, various healthcare-specific entities).
- An **"operator" entity** to serve as both a strategic and tactical coordinator and as a trusted third party between the government and private sectors.

Federal Government

Even though the federal government would not be individually deciding and directing activities in this model, it still has critical leadership and support roles as the preeminent catalyst of the activity. It also has unique qualities that it can bring to bear across the collection of the group's activities:

- Most influential determiner of national priorities
- Power to declare public health emergencies (and to help focus activities during those emergencies)
- Nation's largest sponsor of research
- Holder of enormous amounts of data on a variety of matters
- Unprecedented ability to convene executives from various communities together
- Breadth of piloting environments and opportunities
- Largest and widest audience for publicizing the group's activities and its impact

Federal government activities would need to be coordinated by a White House-led interagency body that leverages proven science and technology (S&T) management concepts and approaches highlighted in the MITRE document *Interagency S&T Leadership*.[6]

Private Sector

Our analyses showed that success would depend on reaching large groups of thought leaders from throughout the extended private sector ecosystem quickly, systematically, and strategically. Rather than taking a shotgun approach of targeting entities directly, the plan instead would be to identify *existing* networks (with diversity of thought, experiences, and geographic locations) to leverage and pull their members into the broader collaboration. We also recognized that each participant's role would vary by their level of commitment and involvement and would generally fall into one of three categories:

[6] D. Blackburn. Interagency S&T Leadership. 2016. MITRE, https://www.mitre.org/sites/default/files/publications/pr-16-0916-interagency-s-and-t-leadership.pdf.

- **Knowledge** – Provide subject-matter experts to aide in strategic planning and to lead or participate in collaborative (involves the most participants).
- **Resources** – Capital investments and assets such as facilities, data, tools, and human capital to facilitate execution.
- **Governance** –These entities would help shape the strategic direction of the collaboration and its supporting activities (involves the least participants).

An important note is that each private sector network and individual participant will need to feel there is sufficient value recovered from their investment(s) in the initiative's activities. This will vary by the category of their involvement and their individual areas of focus in their normal business.

We have seen aspects of this design and related considerations on smaller scales in a variety of contexts, including clinical trials. In the COVID-19 Healthcare Coalition, for example, we learned that given the current difficulties in sharing health data, the ideal model requires options for both centralized and federated capabilities.

MITRE also acted, in the Department of Health and Human Services Office of the Assistant Secretary for Preparedness and Response's (ASPR) COVID-19 Real World Evidence for Monoclonal Antibodies (mAbs) Project, as a trusted third-party data aggregator and analytics team. In collaboration with academic medical centers and care delivery systems, we worked to (1) gather and analyze real-world data to develop real-world evidence (reflected in predictive models) regarding the safety and effectiveness of mAb treatments for COVID-19, including risk stratifications to help prioritize the use of mAbs and (2) identify effective and improved care models, including recommendations for the removal of barriers to accessing and using mAb treatments.

In Europe, several federated learning networks have been built using the DataShield open-source capability.[7] Such networks might decrease the risk for organizations wishing to participate, potentially in low health IT resourced organizations serving diverse and disadvantaged populations. MITRE demonstrated federated learning capabilities during C19HCC famotidine, remdesevir, and convalescent plasma studies and more recently, has developed an internal prototype demonstrating the use of a DataShield network for pandemic response queries using synthetic patient records. MITRE has also been in discussion with commercial vendors to assess the feasibility of similar federated capabilities in the U.S.

<u>Operator</u>

In addition to serving as the trusted third party between the government and private sector, driving them to consensus decisions, the operator entity would also oversee the management and operations of the selected activities. The operator would require a staff (or connected associates) with skills in areas such as program management, communications, strategic partnering, market research, medical technology and business strategy, policy and public administration, legal, finance, contracts, and legislative affairs. The operator would focus on activities such as those listed below:

[7] A. Gaye, et al. DataSHIELD: taking the analysis to the data, not the data to the analysis. 2014. International Journal of Epidemiology, https://doi.org/10.1093/ije/dyu188. Last accessed January 24, 2023.

- Facilitation – Serve as a liaison and formal interface between the White House, federal agencies, and private sector networks.
- Network Management – Build and maintain the partner networks, establishing and nurturing the formal and informal relationships needed to execute the initiative's plans.
- Market Research or Scanning – Engage the network organizations to scan their members to identify trends, issues, and solutions that may impact or influence research initiatives or provide insight into new avenues of investigation.
- Research Agenda – Facilitate and manage the process of assembling and refining the initiative's Research Agenda, combining priorities from the National Science and Technology Council and private sector participants with any relevant trends, issues, or promising approaches learned from market scanning.
- Events and Publications – Design, organize and manage events, programming, and publications that deliver education and information to agencies, network partners, and research teams.
- Research – Engage network partners, spur interest in contributing to research initiatives, and execute research addressing collaboratively identified priorities.
- Data Management – Collect, maintain, and enable sharing (when allowed and appropriate) of data amongst participants. Serve as a trusted third party for sensitive data.
- Demonstration Pilots and Proofs of Concept – Facilitate access to data, research infrastructures, and opportunities within agencies to pilot, conduct proof of concept and demonstrations around research initiatives and potential solutions.
- Reporting – Monitor progress on research initiatives and evaluate and report on outcomes achieved.
- Feedback – Distill insights derived from research and share with agencies and private sector partners to inform future strategy and research priorities; provide input to OSTP and OMB to help strategically plan future strategies and budget requests.
- Communications – Develop a comprehensive communications program that will promote the work and capabilities of the initiative and individual partners, increasing awareness of research initiatives, outcomes, and recommendations.

e. Mechanisms for tracking institutions, networks and sites that might be able to participate in emergency research, to ensure adequate potential for enrollment and adequate geographic coverage, domestically and internationally.
   i. Criteria for establishing a target number and location of sites needed to support clinical trials in case of emergency.

MITRE's recommended approach envisions predominantly focusing on identifying and leveraging existing diverse networks rather than separately tracking and targeting institutions individually. Doing so not only enables economies of scale but also helps ensure these existing activities view the initiative favorably rather than as a threat. The operator entity would be tasked with managing relationships with these networks, which would include collaborating with

leadership to petition their membership for information as well as to gather and organize the returned information for analysis and future tracking.

The target number and location of sites needed to support research should be determined during trial design by experienced evaluators, based on scientific criteria such as sample size and power needed to detect a difference, significance, number of patients and sites/regions impacted, probability and risk of outcomes and end points of interest, and anticipated effect size.

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

In MITRE's recommended model, this would be a task assigned to the operator entity, who would perform the task by joint analysis and obtaining consensus from government and private sector partners. Existing public-private partnerships would be leveraged as part of this planning process.

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

MITRE recommends that the data needed to support emergency clinical trial research should be piloted, prototyped, and moved into the relevant policy and regulatory constructs prior to need. The data should be conformant to a common data model to facilitate the development of study designs and protocols that can be universally implemented. Such data should derive from routine care provision and be used for the monitoring of routine care as frequent use will ensure that the data is available for emergency purposes when needed. MITRE provides additional details in its response to the related "data" RFI.

Quality by design principles informed critical research during the COVID-19 pandemic, such as the RECOVERY trial, are relevant to the conduct of point-of-care trials. The ASPR mAbs study was designed to use existing real-world data collected from the patient's electronic health record, which was then supplemented with additional study data. Regardless of study design, the protocol must specify a common data model and common study endpoints that can be scaled to facilitate more rapid, robust, and valid evidence generation.

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

b. Effective ways to increase diversity among study participants and investigators, and to expand clinical research sites into underserved areas.

One of the most valuable ways of increasing clinical trial diversity is by simplifying trials and reducing their costs.

Data collection is one factor that limits clinical trial diversity. A typical trial includes numerous site visits and vast amounts of data collection (dozens of pages per patient). Those pages of data

collection are burdensome for both trial sites and patients and limit where trials can be conducted as few community sites have the time or resources to collect that much data.

In many cases, simpler trial designs and a quality-by-design approach can reduce the need for data collection. Experts agree that many trials are too complex, and that simpler, streamlined trials would allow us to answer many important clinical questions. This, in turn, will enable us to reach more diverse patients who do not have the time and resources to participate in trials at large academic medical centers.

Another way to reduce data collection burden is to leverage technology. For example, technology can help us embed data collection within the EHR to make data collection less burdensome for clinicians, augment data collected in clinical trials with real-world data obtained from electronic health records and collect data directly from patients. MITRE discusses this in more depth in the accompanying "data" RFI response.

As we make efforts to increase the diversity of clinical trials, we should explicitly benchmark, monitor, and seek to reduce per-patient costs. Clinical trial costs have reached over $40,000 per patient on average; this represents a level of spending and resources that will be difficult to sustain over the course of a pandemic.[8] MITRE has spoken with experts and leaders in clinical trial execution, and there is broad agreement that by simplifying trials and leveraging new tools and technologies we must reduce clinical trial costs in the United States by a factor of ten. If we can make trials less costly, we will have an easier time building, executing, and expanding broad clinical trials that reach beyond the patient population of highly resourced academic medical centers.

3. "Warm Base" Research

Our healthcare system does not have sufficient experience or expertise in conducting point-of-care trials. A robust "warm base" of point-of-care research can help the United States be better-prepared to meet the challenge of a pandemic. Warm base research supports a better clinical trial workforce, better tools for conducting point-of-care trials, more efficient and streamlined processes and technologies, and a broader more inclusive network of clinical trial sites.

Warm base research should address critical public health needs and better outcomes for patients. MITRE recommends that the government identify and support research in critical disease areas and address specific research questions in which point-of-care research can add value. We recommend focusing on research areas that address the following concerns or criteria:

- address disease areas in which there is high health burden and unmet medical need, particularly in vulnerable and underserved communities
- Areas for which there are specific research questions that, if answered, could lead to meaningful benefits to those communities
- Little commercial incentive to carry out the research (i.e., the private sector is unlikely to fund the necessary research)
- Questions that point-of-care approach can be used to answer

[8] T. Moore, et al. Variation in the estimated costs of pivotal clinical benefit trials supporting the US approval of new therapeutic agents, 2015-2017: a cross-sectional study. 2020. BMJ Open, https://bmjopen.bmj.com/content/10/6/e038863. Last accessed January 24, 2023.

Site Considerations. To conduct clinical research, sites must have the tools, technology, and expertise to collect and analyze data for clinical research and share that data using common data standards such as Observational Medical Outcomes Partnership (OMOP) or Fast Healthcare Interoperability Resources (FHIR). While many academic medical centers possess these resources, community sites that are unaccustomed to conducting clinical research may need additional training and support. This support can come in several forms: (1) a warm base research network may wish to provide sites with easy-to-use, accessible, and affordable tools to support embedded data collection and data exchange and (2) training and support for the use of these tools. In certain cases, a centralized study coordinating center can perform certain functions on behalf of research sites, such as remote monitoring and data analysis.

To ensure that research sites can participate in a network and contribute reliable data in a clinical trial, we recommend developing and conducting technology "readiness assessments." These assessments would include "connectathons," simulated data collection and exchange, or other structured interactions with trial sites that would validate sites' ability to collect study data using their electronic health records systems and exchange that data reliably. More broadly, we recommend that a warm-base point-of-care trial network include comprehensive support for new sites that are unaccustomed to conducting clinical research. This support should come in the form of technology assistance, training, workforce development, and financial incentives.

Beyond point-of-care. While point-of-care trials in community settings can answer some research questions, they are not as effective at evaluating investigational therapies. Yet some of the principles of point-of-care trials can be carried into other research areas. More broadly, we recommend building any warm-base network around the concept of embedded platform trials: technology-enabled clinical trials embedded into clinical practice that leverage real-world data, including data collected in electronic health records and from patients own devices, and use AI and machine learning to improve trial design, recruitment, and execution.[9,10,11] These platforms can be readily adapted to conduct research in a pandemic.

REMAP-CAP is one example of such a trial which was readily repurposed into a COVID trial during the pandemic. Within the context of a platform trial, a study can be stood up quickly, and at lower cost than traditional "one-off" trials.[12,13]

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[9] D.Greenbaum. Making Compassionate Use More Useful: Using Real-World Data, Real-World Evidence and Digital Twins to Supplement or Supplant Randomized Controlled Trials. Pacific Symposium on Biocomputing, https://psb.stanford.edu/psb-online/proceedings/psb21/greenbaum.pdf.

[10] O. Inan et al. Digitizing Clinical Trials. 2020. Digital Medicine, https://doi.org/10.1038/s41746-020-0302-y. Last accessed January 23, 2023.

[11] S. Kolluri, et al. Machine Learning and Artificial Intelligence in Pharmaceutical Research and Development: A Review. 2022. the AAPS Journal, https://doi.org/10.1208/s12248-021-00644-3. Last accessed January 23, 2023.

[12] REMAP-CAP Response to the COVID-19 Pandemic. 2022. REMAP-CAP, https://www.remapcap.org/coronavirus. Last accessed January 23, 2023.

[13] M. Neal, et al. Emerging clinical trial designs may accelerate translation in hematology: lessons from COVID-19. 2022. Blood advances, https://ashpublications.org/bloodadvances/article/6/16/4710/485709/Emerging-clinical-trial-designs-may-accelerate. Last accessed January 23, 2023.