Decentralized Trials & Research Alliance

Response to Emergency Clinical Trials RFI (#87 FR 64821)
Submitted to White House Office of Science and Technology Policy (OSTP)
Submitted on behalf of the Decentralized Trials & Research Alliance (DTRA)
Submitted January 27 2023

Background

The Office of Science and Technology Policy (OSTP) has issued a Request for Information (RFI) to ensure that coordinated and large-scale clinical trials can be efficiently carried out to address outbreaks of disease and other emergencies.

The Decentralized Trials and Research Alliance (DTRA) is a non-profit collaboration with over 125 member organizations working together to ease the global adoption of decentralized research methods. DTRA members represent bio-pharmaceutical companies, technology and service providers, site networks and research centers, advocacy groups and government agencies.

The DTRA glossary defines a decentralized clinical trial (DCT) as:

> A clinical trial utilizing technology, processes, and/or services that create the opportunity to reduce or eliminate the need for participants to physically visit a traditional research site.

Of note, DCT is an "umbrella term" and inclusive of many models and archetypes including both fully-decentralized as well as hybrid approaches.

Central to decentralized research is the use of decentralized research methods which the DTRA glossary defines as:

> Decentralized research methods include technologies (telehealth, wearables, remote clinical assessments) as well as processes (home health, local labs, local imaging, delivery of investigational drug product) used to create the opportunity to reduce or eliminate the need for participants to physically visit a traditional research site

As the nature of a pandemic requires limiting travel, quarantine, and reducing load at hospitals and medical centers, clinical trials relied extensively on the use of decentralized research methods during the COVID-19 pandemic. This included both

continuity measures for non-COVID clinical trials initiated prior to the pandemic, as well as planned measures for outpatient trials of COVID-related therapeutics and vaccines.

Likewise, utilizing decentralized trials and research has proven to be an important measure supporting ecosystem goals of improving diversity and representation in clinical research. Clinical trial participation brings burden to all, but that burden may disproportionately create access barriers for those from underserved communities which may be mitigated through decentralized methods.

Our nation's hospitals and health systems will remain a cornerstone of responding to a future medical emergency, but these institutions risk being saturated or inaccessible to support research. A national plan for prospective emergency clinical trials meant to also support diversity and inclusion must include the thoughtful use of decentralized research methods.

Listening Session

On January 23 2023 DTRA hosted a Listening Session for the OSTP RFI. This session included members of the DTRA community along with invited guests from OSTP, the Office of the National Coordinator for Health Information Technology (ONC) and other federal agencies participating in this RFI.

A recording of this listening session may be found at: https://bit.ly/DTRA-ONC-RFI

The listening session included three themes with insights from DTRA members including:

1. *How might decentralized research be used to enhance equitable participation in emergency clinical trials?*
    - Otis Johnson, Clario
    - Ryan Brown, Circuit Clinical
    - Tufia Haddad, Mayo Clinic
    - Kendal Whitlock, Walgreens
2. *How might regulatory flexibility help accelerate emergency clinical trials using decentralized methods?*
    - Mo Ali, Medable
    - Mark Brown, IQVIA
    - Rasika Kalamegham, Genentech
    - Josh Rose, CVS
    - Steve Walker, CSL

3. *How might we develop a pilot or demonstration project to use decentralized research for emergency clinical trials in a 6-12 month timeframe?*
    - Hassan Kadhim, BMS
    - Greg Licholai, ICON
    - Jane Myles, Curebase
    - Caroline Redeker, Advanced Clinical
    - John Reites, Thread

1. Utilize Decentralized Research Methods to Enhance Equitable Participation in Emergency Clinical Trials (ECT)

Intentionality will be a key element in any solutions that are used to enhance equitable participation in trial in any setting, including emergencies. This will require some planning and testing, so that data-driven approaches to improving participant inclusivity can be implemented in ECTs.

a. In order to participate in a clinical trial, one must have the means to be present at a research center with high frequency – often requiring time from work and transportation being needed during traditional business hours. In the course of a pandemic this is particularly challenging for those identified as essential workers. It has been reported that Black and Hispanic people are overrepresented in the essential workforce. Decentralized approaches can bring the trial to these individuals.

b. Patients have trusted relationships with providers in their local communities, and including these providers can help build trust in research. This engagement can also include sharing of results, which is often a missing opportunity to build trust. For those healthcare providers in diverse communities that are interested in serving as an investigator, we must help in providing tools and infrastructure. For other providers in the community that are not in a position to serve as an investigator, decentralized methods can help them provide participation with remote investigators (such as seeing the investigator via video). Particular attention should be paid to Federally Qualified Health Centers and the potential to build their competency to support research for both conventional studies as well as in emergency situations.

c. Researchers can not rely on technology access or they risk marginalizing patients impacted by the digital divide, and in many cases researchers must maintain options for provisioning technology or network access. Technology solutions are rarely one-size-fits-all, and must accompany strategic and active engagement, education and empowerment. In addition, research participants tend to prefer tools and systems that are familiar to them. Building ways to access 'the familiar'

into a clinical trial setting will help address clinical trial participation by underrepresented groups.

d. Incorporating input into study design from representative patients may help tackle structural issues impacting diverse participation. Researchers must focus not only on input about science and trial design, but also on how participants would prefer to participate. Patient insight gathering must be conducted prior to an emergency situation to enable these insights to be applied systematically and repeatedly across trials in an emergency (such as to support a master protocol developed prior to the emergency).

e. Trust is a significant barrier, but often patients of color are simply not being invited to participate. Equity in inviting participation can be mitigated with decentralized partners, such as through retail pharmacy and other trusted partners within diverse communities.

f. Incentives must be aligned to supporting the emergency clinical trial, both for participants and for investigators. For participants, that might include ensuring early access to any treatments that are approved based on data in studies which that patient supported. For investigators, that might include access to data for research purposes beyond the emergency trial setting, or a mechanism to ensure that trial participation for their patients elsewhere will not lead to financial loss, and that they will be fairly paid for their time. Structuring incentives so that they are clear, fair and non-coercive is complex and needs to be addressed prior to any emergency setting, with input from ethics committees and institutional review boarfds.

2. Regulatory Flexibility May Accelerate Emergency Clinical Trials Using Decentralized Methods

a. State licensing requirements for healthcare providers impact the for a study investigator to enroll and monitor research participants across state lines. Ambiguity between supporting research and providing care must be addressed, and the role of an investigator for a clinical trial operating under an FDA Investigational New Drug (IND) application should not be constrained by legacy state medical licensure constraints.

b. The language in regulations and policies must shift from a focus upon “the site” and focus instead on the investigator and the participant, thereby providing flexibility around the location of participation. The concept of a site implies a single location from which the individual may participate, rather than embracing

the more flexible and technology-supported new models for connecting the investigator and the participant.

c. Technology must be deployed to support the investigator with access and currency of information to allow oversight, ensuring investigators are effective, efficient and confident.

d. Form FDA 1572 has supported research for years during the time when all visits took place at known and predictable research sites. The limits of this form were uncovered during the pandemic when locations became far more expansive, and it is often viewed as inhibiting progress in research beyond the pandemic. Modernizing the form FDA 1572 will help researchers go farther in meeting patients in the community – in routine trials as well as in emergencies. The focus and intent of trial documentation must remain on data integrity and clarity of oversight.

e. New digital endpoints will help to create more location flexibility, and require proper qualification and validation to ensure reliable measurements regardless if taking place in the clinic, at home, or some place in between. Such measurements cannot be developed on-demand during an emergency, and increasing clarity of expectations with digital endpoint validation will help researcher sponsors to make early investments in novel measurements (such as digital endpoints) that may prove critical in times of emergencies.

f. Continuing support for electronic source data (eSource) will be a critical ingredient to ensuring that investigators have complete data access and confidence in their ability to fulfill their oversight responsibilities. Where data can be collected electronically agnostic to location, appropriate tools can then ensure the investigator has timely data access and control over integrity while supporting patient privacy and data security.

g. With distance increasing between the participant and a research site, studies will grow dependent upon the ability to access trusted electronic health data with a participant's permission which may be obtained during the informed consent process. FHIR-based standards for extracting study data from the electronic health record will support emergency trials with screening, eligibility, safety monitoring, and measuring efficacy. Interoperability – potentially at international scale – will be critical to realize this opportunity, and technology providers must support flexibility and configurability to enable data interoperability. Such interoperability will support transparency and confidence

in data.

h. Proactive policies for permissioned data sharing will improve data gathering in emergency situations, both for individual participants as well as institutions to choose to share data. Data protections as well as access rights must be explicit for participants, as well as researchers. Currently data access limitations will significantly complicate building an emergency trial-ready data aggregation strategy.

3. Opportunities Exist for Pilots or Demonstration Projects Using Decentralized Research for Emergency Clinical Trials in a 6-12 Month Timeframe

a. Pilot/demonstration design considerations:
   i. Demonstrate a simple design that mimics clinical practice to test an ability to engage a diverse population of patients and providers to participate in research.

   ii. Demonstrate the ability to efficiently populate clinical research data from existing electronic health records, such as through repurposing solutions developed to support the National Institutes of Health All of Us program.

   iii. Develop a scoring system to evaluate the readiness of sites and care settings to rapidly deploy decentralized research methods to reach representative patients for potential emergency clinical trials.

   iv. Develop and demonstrate new incentives for community physicians to educate and engage their patients in research participation (such as novel and compliant reimbursement strategies for research screening).

   v. Develop and disseminate templates for business continuity plans to include within clinical trial protocols to provide proactive planning for emergency situations.

   vi. Develop pathways for pre-approval for areas such as with regulators for conducting specific study assessments remotely via telehealth or with institutional review boards for pre-contracting research investigators. Explore an ability to confirm a list of pre-defined assessments and endpoints to support emergency trial readiness; this may including supporting data flow such as FHIR-enabled data extraction from electronic health records to supplement trial-specific data.

vii. Demonstrate the impact on speed, oversight and data integrity with studies using highly centralized approaches for technology and services as compared with those using technology and capabilities available at the site.

b. Pilot/demonstration population considerations:
   i. Consider focusing on first responders (health/medical, police/fire, military) or essential workers as research participants given their significant role and exposure in the event of an emergency. Note that first responder and essential worker roles are often filled with a higher proportion of underrepresented populations.
   ii. Consider demonstrations that may include therapeutic areas or indications that may be difficult to reach in an emergency situation.

Conclusion

The members of the Decentralized Trials & Research Alliance thank the OSTP and their partners for leading on this important issue for ensuring research in times of crisis, and look forward to opportunities for collaboration in the period beyond the RFI.

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