Summary of Responses to the Network Activation Call for Advancing Clinical Trails Readiness (ACTR)

On October 19, 2023, the ARPANET-H Customer Experience Hub (CX Hub) released a Network Activation Call ("the Call") for Advancing Clinical Trial Readiness (ACTR) Initiative as the first initiative within ARPANET-H Health Innovation Network. The Call drew on the ARPANET-H network to source feedback at scale on program concepts, inform technical and funding approaches, and map the landscape of potential partners. It was designed to meaningfully engage diverse stakeholders, end-users, and non-traditional partners (including beyond the current network membership). More information about this Call can be found at the CX Hub's ACTR Initiative Intake Form Questions. After introducing the ACTR initiative and the Call's engagement approach, this document summarizes the following eight salient themes that emerged from the Call responses.

1. Framing and scoping efforts aimed at advancing clinical trials readiness on a national scale,
2. Working with patients, providers, and other stakeholders as specific studies are planned and implemented,
3. Improving access to clinical trials by underrepresented populations and communities,
4. Utilizing and testing decentralized and hybrid (e.g. with Real World Evidence) trial designs,
5. Developing new technologies that reduce barriers to participation in clinical research by patients and non-traditional trial sites,
6. Applying existent healthcare standards and common data models,
7. Engaging with the FDA, CMS, NIH and ONC to assure regulatory and legal issues are addressed, to achieve complementary goals, and to avoid duplicative efforts, and,
8. Transitioning clinical trial innovations to independent financial sustainability.

The Advancing Clinical Trials Readiness (ACTR) Initiative

The ACTR initiative seeks to improve the nation's ability to conduct clinical trials safely, quickly, and equitably. This is important to advance, integrate, and extend clinical trial capabilities that overcome challenges in evaluating new technologies, therapies, and platforms. Ambitiously, this effort seeks to enable more Americans to take part in a clinical trial within a half hour of their home. The ACTR program will require collaboration across a diverse set of organizations to reach the public more effectively, including populations historically hard to reach, such as those underserved and/or underrepresented in clinical trials.

The ACTR initiative posted a project description for feedback that focuses on five task areas:

Task 1 focuses on accelerating patient enrollment in clinical trials, including efforts to

- Develop computational methods that reduce the manual effort required to identify and enroll clinical trial participants

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- Develop patient-centered consent processes

Task 2 focuses on shifting trials closer to points of care, including efforts to

- Develop new decentralized clinical trial designs
- Identify and incorporate emerging technologies within clinical trial systems to enable faster, less expensive, decentralized trials operating closer to, or at, the point of care
- Devise novel statistical methods and demonstrate ways to use real-world data within a decentralized context

Task 3 focuses on distributing protocols and data collection across dozens of locations, featuring efforts to

- Create a data platform and accompanying software tools to distribute, run, and collect data from a common clinical trial protocol across geographically distributed locations

Task 4 focuses on testing and evaluation

- Project will be guided by use cases and a series of challenges, e.g., detection of adverse events during cancer treatment or recruiting hundreds of patients in a short period of time

Task 5 focuses on transition

- Best-in-class capabilities will be developed to accelerate performance of clinical trials for capabilities emerging from ARPA-H programs

ACTR Network Activation Call Engagement Strategy

The ACTR Initiative utilized a multipronged engagement strategy to seek feedback through responses to a survey with 11 questions (two of which included multiple sub-parts; see the Appendix). More than 200 organizations, representing clinical trial practitioners, research organizations and disease experts, were asked to respond. The Call was also featured on the Customer Experience (CX Hub) website and was viewed on average 995 times per week while the Call was active. Two informational webinars held in November were attended by 381 people and an FAQ was created based on questions raised during the webinars and posted on the public CX Hub site. The Call was also promoted on social media. The response period closed on December 1, 2023.

Call Respondent Overview

The Call closed on December 1, 2023. **149** responses were received and analyzed by the CX Hub and ARPA-H staff. Most responses were from for profit organizations (56%), followed by

institutions of higher learning (24%), non-profit organizations (18%), and public sector affiliated organizations (4%).[1]

- Of the for-profit organizations that responded, 47 responses were from Small Businesses. Of the small businesses, 13 are Women-Owned, 8 are Small Disadvantaged Businesses, 5 are Economically Disadvantaged Women-owned businesses, 4 are Veteran-Owned, 3 are Service-Disabled Veteran-owned, and 1 is a Historically Underutilized Business Zone.
- Of the institutions of higher education, 4 that indicated they were either Hispanic Serving Institutions or Asian American and Native American Pacific Islander Serving Institutions.
- Of the non-profit organizations, 13 are research organizations and 9 were healthcare organizations or systems.
- 28% of responses were from ARPANET-H spokes (confirmed members by the date the Call closed).
- Organizations from 31 states responded to the activation call. The highest number of respondents were headquartered in Texas (where the CX Hub is located), followed by California and Massachusetts (see Figure 1).

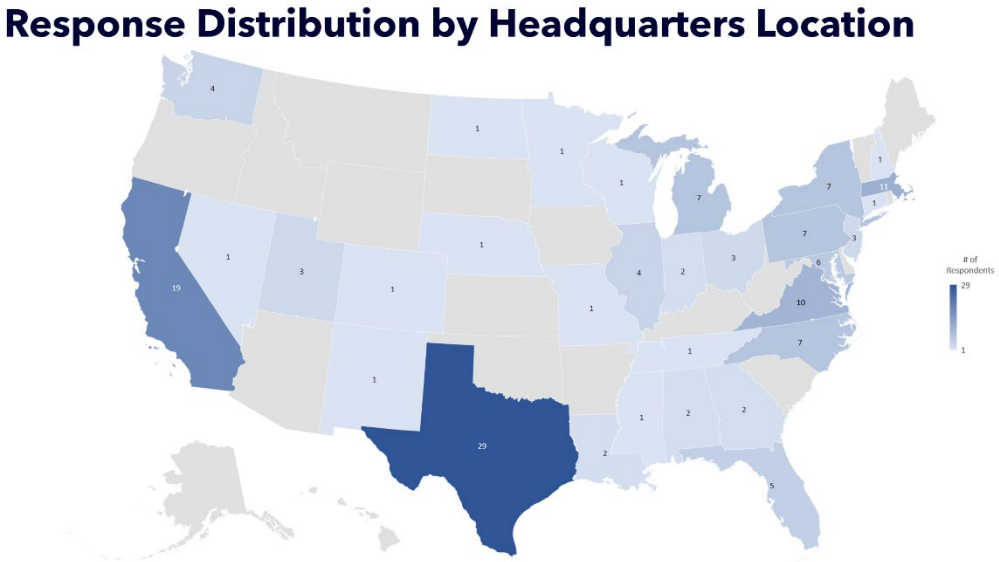

Figure 1[2]

[1] Responses were not mutually exclusive.

[2] Image powered by Bing @ GeoNames, Microsoft, TomTom

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- 38 respondent organizations indicated that they serve all the U.S. The other 80 respondent organizations catchment areas covered the US (N=118) (see Figure 2).

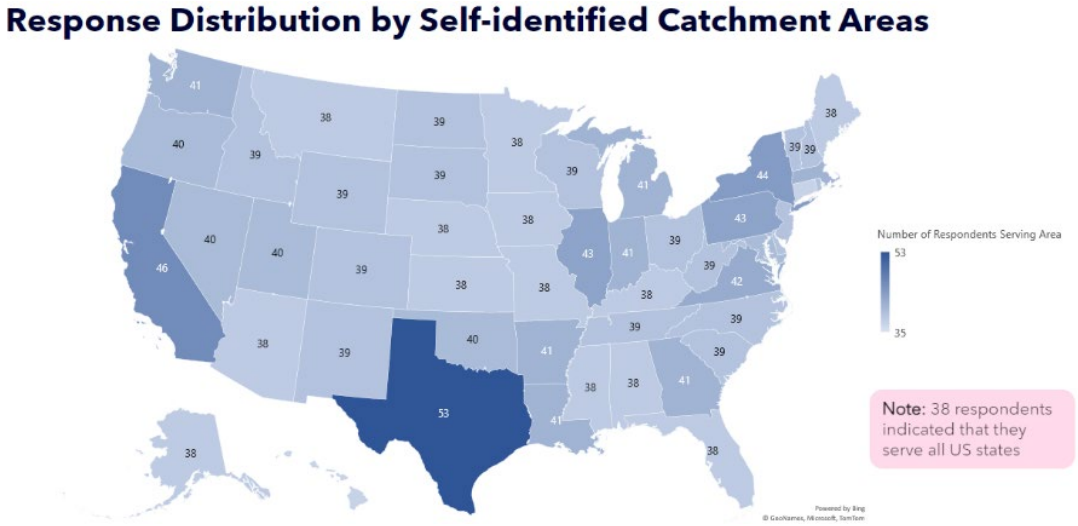

Figure 2[3]

Analysis of Feedback to the Call

Given the variety of sectors represented among respondents, it is not surprising that their diverse points of view yielded heterogenous inputs. From the diverse themes identified during the analysis, ARPA-H identified eight salient themes:

1. Framing and scoping efforts aimed at advancing clinical trials readiness on a national scale,
2. Working with patients, providers, and other stakeholders as specific studies are planned and implemented,
3. Improving access to clinical trials by underrepresented populations and communities,
4. Utilizing and testing decentralized and hybrid (e.g. with Real World Evidence) trial designs,
5. Developing new technologies that reduce barriers to participation in clinical research by patients and non-traditional trial sites,
6. Applying existent healthcare standards and common data models,

[3] Image powered by Bing @ GeoNames, Microsoft, TomTom

7. Engaging with FDA, CMS, NIH and ONC to assure regulatory and legal issues are addressed, to achieve complementary goals, and to avoid duplicative efforts;

8. Transitioning clinical trial innovations to independent financial sustainability.

Theme 1: Framing and Scope

When discussing framing and scope, survey respondents were concerned about the definition of the ACTR Initiative. Given the theme of "accelerating clinical trials," the domain of efforts that might be considered is vast. Respondents mentioned the importance of framing and clarity to scope across multiple questions in the survey.

For example, some respondents noted that the initial framing and scope of the ACTR will be critical to initial and long-term success citing a range of issues. Many respondents recommended developing specific clinical trial use cases. For example, one respondent noted that a "lack of specificity…about the disease states or conditions where ACTR seeks to make an impact could hamper the initiative's success." Another noted that "demonstrating effectiveness through real-world use cases is crucial ... a comprehensive integration from drug discovery to development to post-market will achieve the desired exponential outcomes."

Another component of this theme related to specificity and clarity around populations of interest, with respondents suggesting a range of populations including pediatric populations, patients with chronic conditions, rare or orphan diseases; population-level emergent public health threats; underserved and under-represented populations, etc.

The framing of specific questions for feedback encouraged respondents to inform how the ACTR Initiative might reach beyond a local pilot or prototype to functioning at the national scale. Many respondents commented on novel technologies or frameworks to accelerate clinical trials on the desired scale. One respondent noted that "the advent of scalable and easily adopted novel digital health technologies that decentralize trial activities would be enormously helpful." Another posited that "establishing rigorous testing frameworks to assess the usability, efficiency, and scalability of trial tools and methodologies across diverse healthcare settings is essential." Others discussed approaches they had developed, for example "Digital platforms to streamline patient recruitment are essential... we use pre-programmed algorithms to curate a balanced cohort and prioritize those who can fulfill the research objectives."

Theme 2: Engaging Patients, Providers and Other Stakeholders

Many respondents emphasized the importance of engaging potential study participants, providers, health systems, pharmacies, disease advocacy groups, device and drug developers, and other stakeholders when clinical studies are being designed and implemented. Some emphasized ownership of clinical data by patients and the utility of engaging directly with patients for data sharing or to invite into study participation. Another important theme was the development of networks of sites that allowed for the participation of non-traditional venues for specific applications.

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Theme 3: Improving access for Under-represented Populations and Communities

Addressing underrepresented populations and communities is a critical value for ARPA-H's ACTR initiative, as demonstrated in the framing of the feedback questions. Respondents highlighted successful strategies such as outreach programs in places such as pharmacies and community congregation points. Working with people and facilities that are trusted by diverse potential study volunteers and where underrepresented groups get their care was emphasized. Such facilities often include staff that resemble the communities they serve. One respondent, for example, explained that their "patient navigation team [is comprised] of African Americans, Asian Americans, Hispanic Americans, Native Americans, and Refugees. We have engaged communities directly at Buddhist temples, barbershops, grocery stores, churches, and community health fairs because our team members all come from these communities, so patients feel comfortable with us."

Other respondents described opportunities to use novel approaches such as human-in-the-loop and AI driven methods to improve outreach to a diversity of patients and framing of trial opportunities such as "transferring a greater proportion of study activities directly to the participants … facilitated by adopting remote consent, participant monitoring, videoconference assessments, and at-home phlebotomy services, moving away from the traditional model of bringing participants to trial sites." Opportunities such as these resonate with engaging hard to reach communities by making participation more convenient, utilizing culturally appropriate tools for recruiting and consenting study participants, as well as broadening the geographic access to trials. Finding ways to reduce costs to participants and sites and to compensate study volunteers for their out-of-pocket costs for participation was also recommended by some respondents.

Theme 4: Decentralized and Hybrid Trial Designs

While efforts to decentralize clinical trials existed prior to 2020, decentralized trial designs and technology frameworks to facilitate their execution accelerated greatly because of the COVD-19 pandemic. Recognizing the role that these may play, specific questions on the survey elicited comments on these themes and many organizations commented about them. Some respondents raised red flags and their solutions, for example: "Clinical trials create a wealth of data - both structured and unstructured. Unfortunately, these data types do not operate well together and as a result critical information that informs the design, recruitment and execution of a trial is almost always missed … we believe data interoperability backed by AI is the most vital step to enabling faster, less expensive, and decentralized trials as well as playing a critical role in being able to demonstrate the feasibility of these new approaches." Other respondents appreciated ACTR's opportunity in this space, noting that "establishing a data fabric platform that leverages private Large Language Models (LLMs), data standardization/harmonization and most importantly privacy and security, ARPA-H can take an incredible leap forward in achieving data

interoperability to help physicians and researchers execute more effective, successful, and representative clinical trials."

Another point of emphasis to some respondents is the use of hybrid trial designs that combine conventional clinical trial methods with the use of Real World Evidence (RWE). These types of trials for new drugs and devices will require interaction with regulators and insurers to assure their acceptability and validity.

Theme 5: Developing New Technologies

Many respondents commented on the value of ACTR's developing validated tools for all aspects of clinical trials, both to speed up execution and to reduce costs for participation by patients, providers and sites. Systems that do not require additional effort compared with normal clinical care were noted to be especially important in recruiting sites and providers serving under-resourced communities..

Specific suggestions for the application of new technologies applied to the entire clinical trial pathway – from protocol design, IRB and regulatory approval, identification of sites and potential subjects, consenting subjects, data collection and codification, recording of adverse events, auditing and monitoring of study compliance and source documentation, data cleaning, etc.

Theme 6: Healthcare Standards and Common Data Models

Many respondents were already involved in efforts to develop healthcare standards and common data models to accelerate clinical trials. Their comments presented these experiences and described their value. Some respondents described existing efforts (e.g., efforts within existing HL7 FHIR Accelerators CodeX, Vulcan, and FAST) evaluating the use of standards and common data models in several research focused use cases (e.g., adverse events, trial matching, and consent) that could inform ACTR responses. Respondents overall validated the importance of these efforts, for example noting that "Standardization of data models, broad implementation of FHIR, integration of systems to minimize the manual re-coding and transfer of data to other systems are all critical" and that "establishing a standardized, machine-readable eligibility criteria format and incentivizing pharmaceutical companies to adopt and share comprehensive trial protocols empowers the community." Another respondent noted that "Creating flexible yet structured trial protocols require a robust framework, including the development of universal data collection templates for multi-source data harmonization, ensuring data integrity and comparability."

Theme 7: Engaging with FDA, CMS, NIH and ONC

The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of drugs, biological products, and medical devices. The FDA's evidentiary requirements of clinical trials form a *de facto* standard for medical research. Further, with the increasing digitization of data used for medical research, the FDA has developed guidance on how to leverage real world data for evidence generation in clinical trials.

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Respondents' inputs ranged from simply noting the importance of involving FDA in efforts to accelerate clinical trials, to suggested strategies to accelerate clinical trials in ways that support or improve FDA processes. These included early coordination with FDA on innovative trials design to ensure that "trial results will be considered as valid as data from more traditional clinical trial. Absent that, there will be little willingness to embark on [ACTR], especially from industry partners on a registrational path." For example, one respondent saw potential for "rapid validation (and FDA acceptance of said validation) that routine imaging and laboratory monitoring in clinical trials done at licensed clinical facility is not significantly inferior to the rigid current framework that highly restricts locations for routine clinical monitoring on clinical trials, beyond the recent FDA guidance on decentralized trials." Another raised the opportunity for "Policy reform … to reduce documentation burden and length of time for regulatory approvals as well as physicians' roles on 1572s and licensing across the states to better enable institutions to offer decentralized trials."

The Call placed an emphasis on regulatory considerations that might be challenging to efforts to accelerate clinical trial processes. Respondents noted not only the presence of potential challenges but also provided recommendations on ways that processes, technology, regulatory overhaul, or a combination of the above might offer novel advances in clinical trial design and execution.

Specific pain points were noted around how trials might conduct and ensure informed consent, collection of data from non-clinicians, requirements in the review process of novel pharmaceuticals, and regional variations in the regulatory framework. Respondents provided examples of current hurdles to just-in-time or patient facing consent processes. For example, one respondent noted that "in order to quickly enroll diverse subjects, there must be an automated method for real time consent translation into the subject's native language without the need for IRB review of the translated consent." Another respondent noted that "As we think about disseminating trials to more rural regions, there needs to be more thought on how to supplement the extremely limited resources available at those sites. [Mitigation strategies such as] digital technology will be instrumental in driving clinical trial recruitment, participation, care management, and aggregation of massive data sets." Further, respondents noted multiple key elements needed for the success of the initiative, including "[o]vercoming regulatory barriers, including FDA acceptance of new models for clinical trials, privacy concerns about data sharing, and CMS reimbursements for clinical trials", and "regulatory incentives by ONC and CMS to require disease reporting as part of Meaningful Use Criteria" for disease registries.

CMS and private insurers pay for much of the care rendered to volunteers in clinical trials, but there are still many costs which study participants must pay or that providers must provide at discounted rates, creating barriers to participation for both potential study volunteers and sites.

NIH has several existing programs (such as mCode and CODEX) that are building new technological solutions and addressing many of the same barriers to participation in clinical research, and some participants recommended leveraging those efforts.

Finally, the Office of the National Coordinator for Health Information Technology is charged with the promotion and oversight of a national health information technology infrastructure, and coordination with those efforts was recommended by some respondents.

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Theme 8: Financial Sustainability

Respondents noted the importance of developing a plan for financial sustainability that could enable this effort to transition from public sector funding to private sector support (for example, "The ultimate aim is to set industry standards via the CX Hub, paving the way for future funding and technological breakthroughs in clinical trials").

Some responses highlighted the need to establish industry standards to attract additional funding (potentially from industry stakeholders). One respondent asserted that "70% of studies are delayed due to low patient recruitment. In short, we need to get more from less-and to the benefit of all stakeholders … [we need] information systems and legal support for management of intellectual property, data transparency, publication protocols, and financial structures to appropriately share costs and distribute resulting gains while optimizing patient recruitment, retention, and experience." Other respondents focused on the importance of identifying sustainable funding sources beyond the initial federal funding: "Transition to the real world will require commitment to ongoing maintenance, enhancement, and prioritization of all elements for ACTR moving forward. Funding will need to be earmarked for all such ongoing change and sustainment activities."

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Appendix: Survey Questions

ACTR Intake Form

INITIATIVE DESCRIPTION FEEDBACK (Responses allow 1000 characters):

Please note all questions are optional; only answer what is relevant to you.

1. Which aspects of the initiative description do you see as most vital to meeting the goals of a) enabling faster, less expensive, decentralized, and more representative trials and b) providing demonstrations that show the feasibility and utility of these new approaches?

2. What, if any, components should be added to this initiative description to best enable achievement of the initiative goals? Please note any regulatory considerations.

3a. What existing capabilities, novel innovations, or actions are required for each task to accomplish its goal? Task 1: Enrollment and Consent

3b. What existing capabilities, novel innovations, or actions are required for each task to accomplish its goal? Task 2: Decentralized Trials

3c. What existing capabilities, novel innovations, or actions are required for each task to accomplish its goal? Task 3: Trial Protocols and Data Collection

3d. What existing capabilities, novel innovations, or actions are required for each task to accomplish its goal? Task 4: Test and Evaluation

3e. What existing capabilities, novel innovations, or actions are required for each task to accomplish its goal? Task 5: Transition

4. What, if any, risks/challenges exist in the current framing of the initiative that would prevent it from succeeding? How might these be mitigated?

5a. The Initiative Description Appendix A proposes a progression of notional metrics and milestones that could serve as goal posts to understand the bounds of what's possible today. When framing metrics and milestones, we are interested in understanding what goal posts would

fall into the following categories. What quantitative or qualitative goals would you see as falling within this category: a) Reasonable Baseline Demonstrations

5b. The Initiative Description Appendix A proposes a progression of notional metrics and milestones that could serve as goal posts to understand the bounds of what's possible today. When framing metrics and milestones, we are interested in understanding what goal posts would fall into the following categories. What quantitative or qualitative goals would you see as falling within this category: b) Ambitious, aggressive goals that just might be feasible in a one- or two-year time horizon

5c. The Initiative Description Appendix A proposes a progression of notional metrics and milestones that could serve as goal posts to understand the bounds of what's possible today. When framing metrics and milestones, we are interested in understanding what goal posts would fall into the following categories. What quantitative or qualitative goals would you see as falling within this category: c) Goals that would truly revolutionize the clinical trial space

6. If you are aware of similar efforts already conducted to achieve these goals or analogous efforts in other use-cases, please note these below along with salient lessons learned from those experiences (both positive and negative results).

7. Describe which types of patient populations you can access, why, and how, with an emphasis on traditionally hard-to-reach groups.

8. Describe practical and scientific expertise your team has with: patient navigation, patient counseling, or patient consent for clinical trials.

9. Describe expertise with using and innovating on: electronic health records, clinical trial management systems, or medical data standards.

10. Describe experience you have with trial design, including standard, emerging, and completely novel approaches, and the highest potential approaches for decentralized and pragmatic trials.

11. Describe financial, logistical, regulatory, partnership, consortium membership requirements or other constraints that might prevent you from participating in this effort.

12. Please describe the catchment area that your organization covers (city, county, state, region, etc.)