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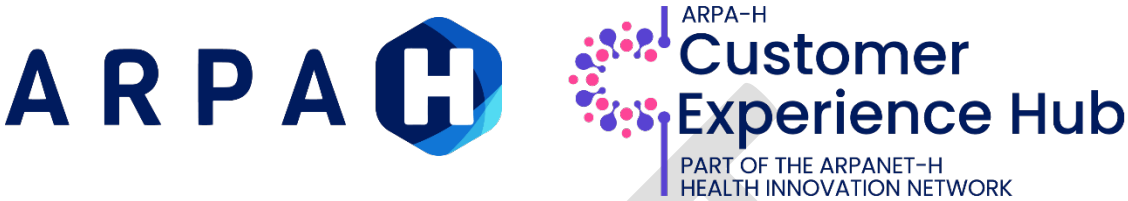
Request for Solutions



Solicitation Number: ARPA-H-CXHUB-25-101

"ADVANCING CLINICAL TRIALS READINESS (ACTR)"

Request for Solutions Issue Date: TBD

Solution Summary Due Date: TBD

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THE ADVANCED RESEARCH PROJECTS AGENCY FOR HEALTH (ARPA-H)
ADVANCING CLINICAL TRIALS READINESS (ACTR) REQUEST FOR SOLUTIONS (RFS)

Solicitation #: ARPA-H-CXHUB-25-101

1. Introduction

1.1 The Advanced Research Projects Agency for Health (ARPA-H):

ARPA-H supports biomedical and health research breakthroughs that can deliver transformative, financially sustainable, and broadly applicable health solutions for everyone. ARPA-H aims to accelerate better health outcomes for everyone, reinforced by its core organizational values that emphasize innovation, agility, and high-impact results. ARPA-H is committed to solving the most challenging health problems by developing Research and Development (R&D) programs that accelerate breakthroughs that improve health outcomes, turning what seems impossible into tangible realities for better health. ARPA-H is pioneering entirely new approaches to address the toughest challenges across the health ecosystem, advancing high-risk, high-impact biomedical and health R&D that cannot be easily achieved through traditional research or commercial activities.

To execute its mission effectively, ARPA-H embraces industry best practices, including due diligence reviews of existing R&D activities, rigorous program design, competitive project selection, thorough performer evaluations, and active program management to ensure optimized and impactful resource use. ARPA-H employs an active portfolio development approach, identifying programs based on clearly defined problems in the health ecosystem, led by the expertise of ARPA-H Program Managers (PMs). This sets ARPA-H apart from other federal health R&D organizations, as ARPA-H does not follow a predetermined or passive portfolio approach. This distinction is crucial, allowing ARPA-H to fund programs with the greatest potential to transform the health ecosystem, rather than aligning funds with projects that offer only incremental improvements.

Finally, ARPA-H's streamlined funding process enables the agency to act swiftly and catalyze cutting-edge biomedical and health R&D. This empowers ARPA-H to rapidly address longstanding problems in the health ecosystem with leading-edge solutions while remaining agile in responding to emergent issues, avoiding delays common in more protracted funding award processes.

1.2 Concise Description of the Initiative:

The Advancing Clinical Trial Readiness (ACTR) Initiative, led by ARPA-H's Resilient Systems Office (RSO), aims to streamline the coordination of decentralized and on-demand clinical trials, lowering barriers to access for all patients. The core focus of the effort is to lay the foundation including the tools, network, and infrastructure necessary for trials to effectively reach at least 90% of Americans within 30 minutes of their homes. By developing technical approaches that facilitate a "network of networks", ACTR will enable Contract Research Organizations (CROs) to interoperate and extend into different non-traditional sites, geographies, and patient populations, making clinical trials more accessible, representative, and cost-effective.

ACTR aims to improve data capture, reduce manual efforts, and increase trial efficiency through three technical areas. These span automating data extraction and synchronization between Electronic Health Records (EHRs) and case report forms (CRFs), standardizing data collection, and enhancing patient enrollment and retention, particularly in underserved and non-traditional sites. These tools will be rigorously tested through virtual demonstrations and real-world evaluations to ensure performance, interoperability, and integration into existing clinical trial systems. For the initial funding opportunity, the expected period of performance will be 12 months. The selected performers will work directly with a Portfolio Lead (PL) at ARPA-H. They will receive an ARPA-H award contracted through the ARPANET-H Customer Experience Hub and the relevant Consortium Management Firm (CMF).

2. Technical Information

2.1.1 Background

Clinical trials are a critical component of the biomedical research pipeline, serving as the primary means by which new drugs, medical devices, and interventions are evaluated for safety and efficacy before they can be approved for widespread use. The data collected from clinical trials forms the basis for regulatory decision-making and informs clinical practice guidelines that shape the standard of care.

However, the current clinical trial ecosystem faces numerous challenges that hinder the efficient and effective conduct of research. One major issue is the lack of interoperability among EHRs, Clinical Trial Management Systems (CTMSs), and other data capture systems. This lack of integration makes it difficult to exchange information seamlessly across different platforms, leading to manual data entry, duplication of efforts, and increased risk of errors. As a result, the process of executing clinical trials becomes more time-consuming, costly, and prone to inaccuracies. The average duration of clinical trials, from initial discovery to full approval of new treatments, is 10 years.[1] Moreover, 80% of clinical trials fail to meet enrollment timelines,[2] and 55% of trials are terminated due to low accrual rates,[2] with most trials relying on manual participant identification, recruitment, and obtaining the consent of potential study volunteers. The cost of recruitment is also a significant burden at an average of $6,500 to recruit one trial participant and $19,500 to replace volunteers who drop out.[3] Combined, 33% of publicly funded trials require time extensions due to missed recruitment goals.[4]

Another significant challenge is the lack of participation of patient populations in clinical trials. Historically, trial participants have been predominantly from urban areas, white[5], male, and older, with demographic profiles that are not always representative of the patient population affected by the diseases being studied. Such skewed participation can lead to an incomplete understanding of how treatments may affect different subgroups and can perpetuate health disparities. Factors such as strict eligibility criteria, limited access to trial sites, and mistrust of the medical research community have contributed to this ongoing problem. The traditional model of conducting clinical trials in academic medical centers or dedicated research facilities also poses barriers to patient participation. Many potential participants may not live near these sites or may face logistical challenges such as transportation, childcare, or time off work. On average, clinical trial participants travel 67 miles to reach a trial site[6]. This limits the ability to reach different communities and impedes patient access to trials.[7]

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[1] https://www.antidote.me/blog/how-long-do-clinical-trial-phases-take#:~:text=This%20process%20can%20take%20a,seven%20years%20of%20that%20time.

[2] Desai M. Recruitment and retention of participants in clinical studies: Critical issues and challenges. Perspect Clin Res. 2020 Apr-Jun;11(2):51-53. doi: 10.4103/picr.PICR_6_20. Epub 2020 May 6. PMID: 32670827; PMCID: PMC7342339. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7342339/

[3] https://mdgroup.com/blog/the-true-cost-of-patient-drop-outs-in-clinical-trials/#:~:text=On%20average%2C%20it%20costs%20%246%2C533,to%20non%2Dcompliance%20is%20%2419%2C533.

[4] Campbell M.K., Snowdon C., Francis D., Elbourne D., McDonald A.M., Knight R., Grant A. Recruitment to randomized trials: strategies for trial enrollment and participation study: the STEPS study. Health Technol. Assess. 2007; 11:105. iii-ix.

[5] Oh, S.S., Galanter, J., Thakur, N., Pino-Yanes, M., Barcelo, N.E., White, M.J., De Bruin, D.M., Greenblatt, R.M., Bibbins-Domingo, K., Wu, A.H. and Borrell, L.N., 2015. Diversity in clinical and biomedical research: a promise yet to be fulfilled. *PLoS medicine*, *12*(12), p.e1001918.

[6] https://www.antidote.me/blog/how-long-do-clinical-trial-phases-take#:~:text=This%20process%20can%20take%20a,seven%20years%20of%20that%20time.

[7] Borno HT, Zhang L, Siegel A, Chang E, Ryan CJ. At What Cost to Clinical Trial Enrollment? A Retrospective Study of Patient Travel Burden in Cancer Clinical Trials. Oncologist. 2018 Oct;23(10):1242-1249. doi: 10.1634/theoncologist.2017-0628. Epub 2018 Apr 26. PMID: 29700209; PMCID: PMC https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6263122/

Furthermore, today's clinical trial networks are structured around the assumption that a single CRO will coordinate the trial across all sites. Therefore, clinical trial infrastructure, e.g., software tools, data infrastructure, data transfer protocols, governance structures, etc., are often developed with the underlying assumption that a single CRO will manage the trial, often using a pre-determined network of sites. This single-CRO structure makes it more challenging to incorporate non-traditional sites that are close to where people live, because each CRO must build its own non-traditional network. In contrast, a more flexible multi-CRO approach would enable CROs to specialize in different types of non-traditional sites, demographics, or geographies.

Additionally, the COVID-19 pandemic has underscored the need for a more agile, responsive, and inclusive clinical trial infrastructure for national emergencies. The urgency to develop safe and effective vaccines and treatments has highlighted the importance of rapidly deploying trials. However, the existing clinical trial ecosystem has struggled to adapt to these demands, revealing the limitations of current processes and technologies.

2.1.2 Technical Description

ACTR will develop a new type of clinical trial infrastructure that will be able to reach 90% of Americans within a half hour of their homes. This infrastructure will be patient-centric and utilize a new sociotechnical systems approach to dramatically improve the accessibility and efficiency of clinical trials. ACTR will start by prototyping novel efficiency-enhancing automations to enable CROs to interoperate and flexibly extend screening, prevention, and pragmatic trial designs into different non-traditional sites, geographies, and populations representative of the diseases being studied. Each CRO will serve as the central node for a network of traditional and/or non-traditional sites and demonstrate the sociotechnical advances necessary for multi-CRO trials to flexibly adapt to the needs of novel trials on demand. The ACTR efficiency-enhancing automation will allow clinical trial networks to expand in a modular way by incorporating additional CROs that can extend the reach to include all relevant populations. The ACTR initiative is particularly interested in fostering the development of automation- and data-related tools to allow inclusion of CROs that specialize in a specific type of non-traditional site, population from a clinical research desert, or geography, so that clinical trial networks can be expanded closer to where Americans live.

The technology-enabled network-of-networks approach will necessitate a new type of clinical trial infrastructure. ACTR performers will develop efficiency-enhancing and data-related tools that enhance the interoperability and level of automation of the software and data infrastructure to enable new, modular multi-CRO trials that extend closer to point of care. Enhancements to reduce the amount of manual labor required to execute trials will be essential for non-traditional sites to participate in trials despite staffing constraints. In addition, enhancing the interoperability of tools will make it possible for CROs that rely on different software tools to work together without needing to change their software infrastructure (in the same way that all CROs can use the internet, even though they may use different web browsers).

The ACTR Initiative has three overarching goals aimed at revolutionizing clinical trials and improving national health preparedness.

1) ACTR aims to establish a robust and efficient clinical trial infrastructure to accelerate clinical innovation and build national health preparedness. ACTR will develop, integrate, and evaluate new

efficiency-enhancing and data-related tools and technologies to enable faster, more representative, and less expensive decentralized clinical trials closer to the point of care, with the goal of making trial sites accessible to 90% of all Americans within 30 minutes of their homes. This will involve developing innovative approaches to automate data extraction and synchronization between EHRs and Case Report Forms (CRFs), evaluating the use of emerging standards to enable the gathering of structured data necessary for analysis, and developing and testing new technologies and tools for the standardization of common protocol and CRF elements. The use of AI/ML tools to automate data collection and curation will enable federated collaboration and accelerate research discoveries, streamlining the process of data capture and management, reducing manual efforts, and increasing efficiency and accuracy. Achieving these goals will result in capabilities that demonstrate new ways to rapidly execute more representative and distributed clinical trials.

2) ACTR will develop innovative methods and tools to accelerate study volunteer enrollment and consent, enhancing patient care through clinical trials that are more representative of the entire U.S. population, including those living in rural communities.
This will involve the development and testing of new technologies and tools for the identification of eligible study volunteers, individualized and culturally appropriate consent processes, and study volunteer engagement and retention. These advancements will help to increase the speed of enrollment, representative demographics of trial participants, and retain trial participants, especially those in clinical research deserts.

3) ACTR will create novel efficiency-enhancing tools and infrastructure for decentralized trials that integrate engagement and collaboration technology to reduce barriers to participation in rural and underserved areas. ACTR will seek innovative network-of-network technology and tools to enable successful clinical trials that span remote and non-traditional locations. These advancements will facilitate the execution of trials in a decentralized manner, reducing barriers to participation.

ACTR will develop, evaluate, and integrate new tools and technologies to enable faster, more representative (across geography, age, sex, gender, race, ethnicity, socioeconomic status), less expensive, and decentralized trials closer to/at the point of care. Advances in Artificial Intelligence/Machine Learning (AI/ML) increasingly adopted data standards (e.g., Fast Healthcare Interoperability Resources (FHIR), Clinical Data Interchange Standards Consortium (CDISC)) to enable sharing of siloed and unharmonized healthcare data (a current focus of work by CDISC), hold promise for increasing the speed, representativeness, and decreasing cost of clinical trials. The project will culminate with compelling demonstrations of the newly developed efficiency-enhancing tools and methods that show regulators, evaluators, EHR vendors, and the pharmaceutical industry the feasibility and utility of rapid, representative, and decentralized trials enabled through the use of trustworthy data. This newly enabled clinical trial framework will be critical for public health response, including in emergency outbreaks or pandemics, and could drive more systemic improvements in the approach to clinical research (including among industry sponsors) that will make better use of scarce resources, such as research funding, industry investments, and the time and physical participation of patients. ACTR outcomes will help shape regulatory science by demonstrating the amount and type of structure needed in clinical trial design to generate actionable, generalizable evidence – e.g., how much "noise" can be tolerated, how much we can rely on EHRs to inform clinical trial design, identify candidates, and integrate with CRFs, and how close trials can be run to the treatment setting.

Solutions proposing new brick and mortar infrastructure are out of scope as are those that solely reuse existing approaches to IT infrastructure without enabling higher levels of interoperability across CROs that do not traditionally work together. Instead, proposed approaches should drive advances in the ability for multiple CROs to contribute to clinical trials in a flexible plug-and-play manner and reduce the amount of manual effort required to run accessible clinical trials at non-traditional sites.

2.1.3 National Health Impact: A Pathway to Improve Health Outcomes

The current state of the clinical trial ecosystem in the United States has significant negative impacts on national health. The COVID-19 pandemic emphasized the need for a more agile, responsive, and inclusive clinical trial infrastructure; however, the existing clinical trial ecosystem has struggled to adapt to these demands, revealing the limitations of current processes and technologies. The lack of representative patient populations in clinical trials has serious implications for evaluating treatments in representative populations and costs the U.S. billions of dollars annually due to early deaths and poor health.[8] Additionally, 33% of publicly funded trials require time extensions due to missed recruitment goals.[9]

Recruitment is also a major trial expense, with costs of $6,533 to recruit one patient and $19,533 to replace a patient who drops out,[10] and estimated costs to sponsors between $600,000 and $8 million per day for each patient who drops out.[11] These high costs contribute to the overall expense of healthcare and may limit the number of promising treatments that can be advanced through the pipeline. Moreover, during the COVID-19 pandemic, there was a 74% decrease in the average number of new patients entering trials in 2020 partially due to a lack of nationwide clinical trial infrastructure including tools for recruiting remotely.[12] Furthermore, cardiovascular disease is expected to cause more than 23.6 million deaths per year by 2030, while drug innovation is lagging, large variations in outcomes exist, and cardiovascular drug costs continue to rise; large population trials are needed to curb this trend. [13]

The lack of representative patient participation in clinical trials has serious implications for the evaluation of treatments in representative populations. Clinical trials often fail to mirror the heterogeneity of the U.S. population, with participants typically representing only a small segment.[14]This lack of representation can lead to an incomplete understanding of how treatments may affect different subgroups and can perpetuate health disparities. For example, Black women are 40% more likely to die of breast cancer than white women,

[8] https://healthpolicy.usc.edu/article/lack-of-diversity-in-clinical-trials-costs-billions-of-dollars-incentives-can-spur-innovation/

[9] Campbell M.K., Snowdon C., Francis D., Elbourne D., McDonald A.M., Knight R., Grant A. Recruitment to randomized trials: strategies for trial enrollment and participation study: the STEPS study. Health Technol. Assess. 2007; 11:105. iii-ix.

[10] https://www.cellandgene.com/doc/clinical-trial-recruitment-001#~:text=Considering%20that%20costs%20an,minimize%20patient%20dropout%20after%20enrollment

[11] Examination of the Clinical Trial Costs and Barriers to Drug Development. Office of the Assistant Secretary for Planning and Evaluation Report. July 24, 2014. sApe.hhs.gov/reports/examination-clinical-trial-costs-barriers-drug-development-0.

[12] Sathian B, Asim M, Banerjee I, Pizarro AB, Roy B, van Teijlingen ER, do Nascimento IJB, Alhamad HK. Impact of COVID-19 on clinical trials and clinical research: A systematic review. Nepal J Epidemiol. 2020 Sep 30;10(3):878-887. doi: 10.3126/nje. v10i3.31622. PMID: 33042591; PMCID: PMC7538012. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7538012/

[13] Bowman L, Weidinger F, Albert MA, et al. Randomized trials fit for the 21st century. A joint opinion from the European Society of Cardiology, American Heart Association, American College of Cardiology, and the World Heart Federation. European Heart Journal. 2022;44. https://doi.org/10.1093/eurheartj/ehac633

[14] Ford I, Norrie J. The Changing Face of Clinical Trials: Pragmatic Trials. New England Journal of Medicine. 2016;375(5):454-463. https://www.nejm.org/doi/10.1056/NEJMra1510059

highlighting the urgent need for more inclusive evaluations of treatments.[15] In addition, there is variation in breast cancer mortality rates and in the Black-White breast cancer mortality disparity by geography within the United States.[16] Breast cancer was the leading cause of cancer death in women (surpassing lung cancer) in four Southern and two Midwestern states among blacks and in Utah among whites during 2016-2017.[17] Geographic diversity is also important in clinical trials since people living in different locations may be exposed to varying levels of pollutants or environmental toxins which could influence the effectiveness of pharmacological therapies and potential side effects.[18] Distributed sites in a nationwide clinical trial network and building trust through culturally relevant patient engagement will be crucial in addressing gaps in trial participation amongst patient populations. The cost of morbidity, mortality, and loss of work resulting from disparities in diabetes care alone is projected to reach $5 trillion through 2050.[19]

If ACTR is successful, it could have significant positive impacts on national health. By reducing the costs and increasing the efficiency of clinical trials, more resources could be allocated to advancing a greater number of innovative treatments through the pipeline. This could accelerate the development of new drugs, devices, and interventions, ultimately providing patients with more options and potentially better outcomes. For example, large-scale clinical trials that measured the safety and effectiveness of statin drugs have saved an estimated $1.3 trillion, resulted in 40K fewer deaths, 60K fewer hospitalizations, and 22K fewer strokes.[20] If successful, ACTR will increase the speed, reduce costs, and increase the patient representation and overall volume of clinical trials in the U.S., accelerating progress toward better treatments and more options for patients. The modular approach that ACTR tools enable will also create a sustainable way to run the large decentralized trials needed to evaluate screening technologies and population health approaches that can reduce healthcare costs and improve health outcomes at the population level. If the ACTR efficiency-enhancing tools help speed products and therapies through clinical trials and at less expense, the effort may enable commercial companies to reduce the cost of healthcare treatments to patients, payors, and to the taxpayer.

By improving the representation of patient populations in clinical trials, ACTR could help to address health disparities and ensure that research findings are more applicable to the broader U.S. population. This increased representation could lead to a better understanding of how treatments may affect different subgroups and could inform more targeted personalized approaches to healthcare. Improvements in the representativeness of clinical trials would further enable the applicability of results to more people in absolute numbers as well as a greater proportion of the U.S. population, both improving overall health and reducing health inequities. By actively engaging underrepresented communities and reducing barriers to participation, ACTR could help to build trust in the medical research enterprise and address gaps in access. The potential impact of such efforts is exemplified by the COVID-19 RECOVERY trial in the U.K., which rapidly

[15] Sathian B, Asim M, Banerjee I, Pizarro AB, Roy B, van Teijlingen ER, do Nascimento IJB, Alhamad HK. Impact of COVID-19 on clinical trials and clinical research: A systematic review. Nepal J Epidemiol. 2020 Sep 30;10(3):878-887. doi: 10.3126/nje. v10i3.31622. PMID: 33042591; PMCID: PMC7538012. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7538012/

[16] Kaur, M., Joshu, C.E., Visvanathan, K. and Connor, A.E., 2022. Trends in breast cancer incidence rates by race/ethnicity: Patterns by stage, socioeconomic position, and geography in the United States, 1999-2017. Cancer, 128(5), pp.1015-1023.

[17] DeSantis, C.E., Ma, J., Gaudet, M.M., Newman, L.A., Miller, K.D., Goding Sauer, A., Jemal, A. and Siegel, R.L., 2019. Breast cancer statistics, 2019. CA: a cancer journal for clinicians, 69(6), pp.438-451.

[18] https://pmc.ncbi.nim.nih.gov

[19] https://www.forbes.com/sites/forbesbusinesscouncil/2024/02/01/underrepresentation-in-clinical-research-and-its-impact-on-health-outcomes/#:~:text=For%20example%2C%20a%20committee%20found,to%20reach%20even%20higher%20costs.

[20] The large social value resulting from use of statins warrants steps to improve adherence and broaden treatment - PubMed (nih.gov)

demonstrated (within 3 months of the pandemic's onset) that dexamethasone reduced deaths by 33% in ventilated patients, ultimately saving an estimated 500K – 2M lives worldwide.[21]

2.1.4 Structure and Technical Areas

ACTR seeks to leverage emerging technologies to enhance system coordination and connectivity, and achieve a transformed clinical trial infrastructure that reaches patients where they are. The program will support two or more Contract Research Organizations working in concert with one another, each specializing in different types of clinical sites and focused on the recruitment of different patient populations (e.g. academic, non-traditional non-academic, urban/rural, different racial and ethnic groups), resulting in the creation of a network-of-networks supported by CRO and clinical trial infrastructure. By leveraging health data standards, high quality interoperable patient data, and standard clinical trial protocols in real-world clinical trial settings, expansion of research capabilities can extend to more varied geographic settings and underserved patient populations, while lowering site and provider burden, reducing costs, and streamlining today's heavily manual and labor-intensive research processes.

2.1.5 ACTR Technical Areas

ACTR comprises three Technical Areas (TAs) that will develop, refine, and integrate efficiency-enhancing tools designed to transform clinical trial infrastructure and move it closer to the point of care. Tools developed will be pressure tested and evaluated within real-world clinical contexts in partnership with appropriate stakeholders as outlined in the Independent Verification & Validation (IV&V) and technology transition strategies.

The TAs outlined below focus on advances in the automation, data infrastructure, and software infrastructure necessary to support multi-CRO clinical trials. Nonetheless, successful clinical trials rely on networks of human experts and study volunteers who forge strong relationships and cultural support structures across organizational boundaries. Therefore, the IV&V strategy and transition sections discuss changes to business models, cultural norms, and governance structures that will play a critical role in the sociotechnical infrastructure required to enable decentralized multi-CRO trials at non-traditional sites.

- **TA1 – Automatic Clinical Trial Data Prompting & Extraction**: Develop innovative tools and approaches to automate data extraction and synchronization between EHRs and CRFs, while standardizing data collection processes and elements to improve efficiency and accuracy. This includes implementing unidirectional and bidirectional data flows to streamline data capture, enhance coordination among trial sites, and adjust what data is collected across decentralized clinical trials. Ultimately, TA1 aims to reduce manual efforts, increase trial efficiency, and facilitate the integration of real-world data into clinical research.
- **TA2 – Research Participant Identification & Engagement:** Develop innovative methods and tools to accelerate patient enrollment and consent and enable trials that are more representative of the U.S. population.

[21] https://www.recoverytrial.net/files/recovery_dexamethasone_statement_160620_v2final.pdf

  - **TA2.1 - Research Participant Identification:** Develop algorithms and approaches to accelerate the identification of potential study volunteers and create solutions that allow participating study sites to search their own records to efficiently identify eligible study participants, while ensuring that the solutions developed are accessible and usable by potential study volunteers and sites.
  - **TA2.2 - Culturally Appropriate Consenting:** Create clear and accessible consent processes for specific data uses and tailored to individual educational and cultural backgrounds, using adaptive methods with real-time translation, promoting informed decision-making.
  - **TA2.3 - Engagement and Retention:** Develop solutions that continuously engage study volunteers, provide opportunities for them to ask questions, learn about the study, and report outcomes, and create tools to identify study participants most likely to drop out so that interventions can be designed to improve retention of study participants.
- **TA3 – Trial-Grade Data Validation and Auditing:** Develop technologies that improve data completeness and accuracy and study audits – i.e. confirmation of regulatory compliance - more automatically. These tools will improve efficiency and reduce costs, thus facilitating the participation of underserved areas and the people they serve.

All tools will be evaluated as part of a virtual demonstration of the tool performance across two or more use cases. Once the tools have been demonstrated and evaluated in virtual test environments, a subset of performer tools will be selected for evaluation within real-world clinical trials. CROs will play a key role in real-world evaluation. ACTR will focus on engaging CROs with non-traditional sites that are more accessible to the average American's place of residence. For example, 91% of Americans live within a half hour of an imaging center and 90% live within a half hour of a pharmacy, making imaging centers and pharmacies potential key targets for real-world evaluation of ACTR tools.

Each Solution Summary responsive to this Solicitation must address a single, entire Technical Area (TA) (i.e., TA1, TA2, or TA3), a single designated sub-TA (i.e., TA2.1, TA2.2, or TA2.3), or any combination of full TAs and/or designated sub-TAs. Proposers may team with other qualified proposers as described below in order to respond to the targeted TA or sub-TA. Proposers are expected to develop technologies that are largely generalizable across clinical trials, regardless of type or domain.

TA1: Automatic Trial Data Prompting & Extraction

TA1 Objectives

TA1 seeks to develop tools to enable decentralized trials to be efficiently conducted closer to the point of care, while dramatically improving the speed and resource efficiency of conducting clinical trials. TA1 tools must be designed to support a novel multi-CRO approach that accelerates data collection at a variety of non-traditional sites. Performers for TA1 will develop innovative tools to automate data extraction and synchronization between EHRs and CRFs while evaluating the use of emerging standards to enable the gathering of structured data necessary for analysis. Products developed under this TA will streamline the process of data capture and management, reducing manual efforts and increasing efficiency and accuracy. TA1 addresses both the standardization of common protocol and CRF elements and the use of AI/ML tools to automate data collection, enabling federated collaboration and accelerating research findings. A key component of this effort is unlocking the efficient extraction and standardization of data from existing trial site

workflows without altering the user interface or workflow. This approach aims to take routine data and turn it into clean trial data that will be acceptable to the study sponsor or regulatory agency, expanding the data available with minimal addition to manual work or trial expense, utilizing the clinical workflow as much as possible without additional data entry. Additionally, TA1 aims to allow CROs to seamlessly collect new data from trial sites in a standardized manner thereby enhancing coordination and unification of trial methodology across disparate CROs and sites.

TA1 Innovations & Deliverables

TA1 will develop unidirectional tools to leverage existing real-world data from EHRs for comparators and control groups, making clinical trials faster and more resource efficient. The most significant cost in clinical trials is the personnel required for collecting participant consent and entering data, tasks that currently disrupt clinical workflows and serve as a disincentive for sites and clinicians to participate in clinical trials. By automating data extraction and synchronization between EHRs and CRFs, TA1 aims to significantly reduce the human time required for these tasks. This automation will streamline the process, reduce the burden on clinical workflows, and make participation in clinical trials easier and more attractive for participating site personnel. Additionally, these unidirectional data extraction tools (pull-only) will also allow for randomization, such as cluster randomization, and enable sites to use real-world data to derive comparator arms, eliminating the need to enroll control populations in clinical trials.

TA1 will also create bidirectional data flow tools that allow CROs to push critical modifications to the front-end User-Interface (UI) at trial sites, prompting personnel to collect new data in a minimally invasive manner (e.g., addition of a field asking whether a patient is experiencing signs of respiratory illness to screen for prevalence of an emerging infectious disease). By seamlessly integrating these tools into clinician and retail workflows, TA1 will dramatically reduce the manual labor associated with trial data collection, which poses a barrier to trial participation. This may enable more sites, especially decentralized non-traditional sites, to participate in clinical trials and ensure that the data collected in trials is representative of historically underserved populations. This will foster a more connected and collaborative ecosystem for clinical trials and ultimately enable the development of more representative therapies. To achieve this seamless trial data collection, TA1 tools will adopt machine-readable data formats, ontologies, and/or executable clinical protocols to enable automated support, workflow, and process requirements for trial activation with a combined goal of reducing clinical trial overhead expenses and manual labor. There are numerous potential technical approaches to achieve the seamless and semi-automated data collection across multiple sites and CROs required for TA1. Proposers are encouraged to outline compelling and innovative strategies to standardize data elements and vocabularies to ensure consistency and interoperability across different studies and therapeutic areas. Solution summaries will advance open-source software tools to distribute, run, and collect data from machine-readable clinical trial protocols, harmonizing relevant data from CTMSs and participants' EHR records. Techniques of interest include, but are not limited to, advanced NLP algorithms, machine learning models, and deep learning techniques such as transformer-based models, and proposers are encouraged to describe novel adaptations to accurately extract and map clinical data elements from EHRs to standardized clinical data management systems (CDMs) and CRFs. Solution summaries will describe how privacy-preserving tools, such as differential privacy and secure computation, will be leveraged to de-identify data, provide quality assurance, protect information provenance, and enable widespread sharing of clinical trial study data for rapid re-analysis. In aggregate, the

proposed TA1 approach should unlock new capabilities, such as the rapid assembly of consistent, unified, and shareable study materials; reducing study start-up times, improving trial efficiency, and facilitating cross-study comparisons and meta-analyses.

TA1 solution summaries must provide a technical plan describing how the proposer will develop or adapt a tool that meets aggressive performance metrics for the following objectives:

1. Automate extraction and mapping clinical data elements from EHRs to standardized CDMs and CRFs, with a high degree of accuracy, using repeatable processes that scale, with easy-to-understand user interfaces to support non-traditional sites.
2. Build on and, if necessary, extend emerging data models, data standards, and common Application Programming Interfaces (APIs), such as the FHIR Questionnaire and Questionnaire Response, which enable the gathering of structured, hierarchical data necessary for analysis.
3. Support seamless data collection and real-time monitoring of participant outcomes, leveraging technologies which may include wearables, telemedicine, and home health monitoring devices, allowing CROs to rapidly collect new data that is not otherwise present in the EHR or site workflow.
4. Demonstrate bidirectional communication of protocols, protocol updates, and trial data in a manner that minimizes the human labor required to adjust clinical protocols.
5. Work with other performers to converge on common data standards and APIs that will enable interoperability across multiple CROs and clinical sites, even when they leverage different software solutions.

TA2: Research Participant Identification & Engagement

TA2 Overarching Objectives

TA2 seeks to develop innovative methods and tools that accelerate patient enrollment and consent processes, ultimately leading to clinical trials that are more representative of the U.S. This goal encompasses three key areas: TA2.1 focuses on the fast identification of eligible and representative study volunteers; TA2.2 aims to create individualized and culturally appropriate consent processes and forms; and TA2.3 seeks to engage and retain trial participants, especially those from underrepresented groups, throughout the duration of the clinical trial.

TA2.1: Research Participant Identification

TA2.1 Objectives

TA2.1 aims to develop algorithms and approaches that reduce the time and resources required to identify and enroll clinical trial participants representative of the diseases being studied, allowing participating study sites to efficiently search their own records and identify eligible study participants within their patient population. However, current technical limitations hinder this process. The lack of interoperability between EHRs and CTMSs makes it difficult to efficiently search for and match potential participants to trials. Manual chart reviews and ad hoc screening processes are labor-intensive and may miss eligible candidates, particularly those from underrepresented groups.

TA2.1 Innovations & Deliverables

TA2.1 will develop innovations that extend and enhance existing NLP technologies. To achieve this, TA2.1 may use advanced machine learning techniques, including but not limited to deep learning and transfer learning, to improve the accuracy of information extraction and classification tasks. Proposers are encouraged to describe in detail strategies for capturing relationships between medical concepts and approaches for standardizing terminologies used across different EHR systems, which may involve techniques including, but not limited to domain-specific ontologies and knowledge bases. Solution summaries will outline innovative strategies for integrating structured EHR data, such as diagnosis codes and laboratory results, to provide a more comprehensive view of a patient's health status and eligibility for specific clinical trials. Proposers are encouraged to outline compelling strategies for analyzing EHR data across multiple healthcare organizations without compromising patient confidentiality. Privacy-preserving techniques of interest may include but are not limited to federated learning and differential privacy. Taken together, the proposed TA2.1 approach should improve Natural Language Processing (NLP) technologies for EHR analysis to more quickly and accurately identify potential study volunteers based on specific inclusion and exclusion criteria, leading to faster enrollment and more representative patient populations in clinical trials.

TA2.1 solution summaries must provide a technical plan describing how the proposer will develop or adapt a tool that meets aggressive performance metrics for the following objectives:

1. Improve ability for study designers to generate computable screening, inclusion, and exclusion criteria or other computable criteria that may be used to identify potential study volunteers.
2. Quickly and accurately identify potential study volunteers based on specific inclusion and exclusion criteria across multiple EHR systems and platforms, leading to faster enrollment, more representative patient populations in clinical trials, and reduced manual labor.
    a. Support use of structured EHR data to automatically identify potential study volunteers who may meet the study's screening and inclusion criteria.
    b. Identification of potential study volunteers should be automated to the extent possible.
3. Improve the accuracy of information extraction and classification tasks using advanced machine learning techniques, such as deep learning.
4. Alert investigators when potential study volunteers are identified.
5. Work with other performers to converge on common data standards and APIs that will enable interoperability across multiple CROs and clinical sites, even when they leverage different software solutions.

TA2.2: Culturally Appropriate Consenting

TA2.2 Objectives

TA2.2 aims to create clear and accessible consent processes tailored to individual educational and cultural backgrounds, promoting informed decision-making. However, current technical limitations hinder this process. Consent documents are often lengthy, filled with technical jargon, and not tailored to the individual's language, literacy level, or cultural background. Additionally, obtaining patient consent for a trial

is a similarly manual and time-intensive process. The consenting process is intended primarily to describe a trial's risks and benefits comprehensively, but does not always ensure that potential study volunteers have an easy decision-making experience or that they understand a trial's goals with complete clarity. The lack of interactive, multimedia tools to explain trial procedures and risks and to answer questions in a culturally appropriate manner can lead to confusion and mistrust among potential participants.

TA2.2 Innovations & Deliverables

TA2.2 will extend and enhance existing translation and localization technologies through real-time production of consent forms that match and suit individual participant language, educational level, and cultural factors. Proposers are encouraged to outline compelling and innovative strategies for customizing consent processes to each participant, considering their specific needs and preferences. Techniques of interest include adaptive methods with real-time translation. Solution summaries will describe strategies for providing answers to specific participant questions, when appropriate, without a human involved. Proposers are encouraged to outline innovative approaches for analyzing and simplifying the language used in consent documents, making them more accessible and understandable to a broader range of participants. Techniques of interest include but are not limited to natural language processing and machine learning. Solution summaries will advance multimedia tools to present information in engaging and intuitive ways, helping participants to better understand the risks and benefits of the clinical trial. Proposers are encouraged to describe compelling methods that will streamline consenting for specified data uses, including additional research, while ensuring the security and privacy of participant data. In aggregate, the proposed TA2.2 approach should create a more personalized, accessible, and secure consent process that builds trust and increases participation in clinical trials among populations that are representative of the diseases being studied.

TA2.2 solution summaries must provide a technical plan describing how the proposer will develop or adapt a tool that meets aggressive performance metrics for the following objectives:

1. Support electronic, verbal, and written consent for trial participants.
2. Obtain patient consent by applying relevant best practices and guidance such as FDA's guidance, "Key Information and Facilitating Informed Consent."[22]
3. Extend and enhance existing translation and localization technologies through real-time production of consent forms that match and suit individual participant language, educational level, and cultural factors to the extent possible.
4. Enable customized consent process for each participant or participant demographic, with attention to their specific needs and preferences, subject to Institutional Review Board (IRB) approval.
5. Provide answers to participants' specific questions, when appropriate, without a human involved.
6. Analyze and simplify the language used in consent documents, making them more accessible and understandable to a broader range of participants using automated techniques; for example, using natural language processing and/or machine learning techniques.
7. Present information in engaging and intuitive ways, using interactive, multimedia tools, to help participants better understand the risks and benefits of the clinical trial.
8. Simplify and automate consent workflow processes to reduce the burden on sites.

[22] Key Information and Facilitating Understanding in Informed Consent Guidance for Sponsors, Investigators, and Institutional Review Boards | FDA

9. Solution summaries will describe approaches for establishing consent based on a patient's permitted use of the data rather than for a specific study alone, allowing secondary use of the data in a research context.
10. Work with other performers to converge on common data standards and APIs that will enable interoperability across multiple CROs and clinical sites, even when they leverage different software solutions.

TA2.3: Engagement and Retention

TA2.3 Objectives

TA2.3 aims to develop solutions that continuously engage study volunteers, providing opportunities for them to ask questions, learn about the study, and report outcomes, fostering a sense of valued contribution and improving participant retention. However, current technical limitations hinder this process. Traditional methods of communication, such as phone calls and mailings, may not be effective in keeping participants informed and motivated. The lack of personalized, culturally relevant engagement strategies can contribute to high dropout rates and missing data.

TA2.3 Innovations & Deliverables

TA2.3 will develop tools that offer an engaging, personalized and convenient experience to trial participants. Techniques of interest include, but are not limited to, advanced algorithms for personalized push and pull triggers, reminders, and feedback based on individual participant preferences and behaviors. Proposers are encouraged to describe potential mechanisms by which their tool could be adapted to leverage wearables, telemedicine, and home health monitoring devices to enable seamless data collection and real-time monitoring of participant outcomes. Solution summaries will describe innovative methods for providing study-specific and general medical information tailored to each participant's needs and preferences. Approaches of interest include but are not limited to personalized patient education portals and chatbots. Proposers are encouraged to outline techniques, which may include but are not limited to machine learning, for identifying study participants most likely to drop out, allowing for targeted interventions to improve retention, particularly among populations that are representative of the diseases being studied. Taken together, the proposed TA2.3 approach should develop novel and effective ways to customize material for targeted dissemination with the goal of retaining participants through the duration of a clinical trial.

TA2.3 solution summaries must provide a technical plan describing how the proposer will develop or adapt a tool that meets aggressive performance metrics for the following objectives:

1. Employ novel methods (e.g., text-based) to engage and communicate with participants during the trial.
2. Individualization to participant preferences and behaviors using approaches which may include push and pull triggers and reminders.
3. Provide study-specific and general medical information tailored to each participant's needs and preferences using approaches which may include personalized patient education portals and chatbots.
4. Identify study participants most likely to drop out, allowing for targeted interventions to improve retention.

5. Work with other performers to converge on common data standards and APIs that will enable interoperability across multiple CROs and clinical sites, even when they leverage different software solutions.

TA3: Trial-Grade Data Validation and Auditing

TA3 Objectives

TA3 aims to dramatically improve the efficiency and effectiveness of maintaining trial data integrity across decentralized and non-traditional sites. Data curation is a process by which data are cleaned, organized, indexed, annotated, and preserved after acquisition so they can be accessed, shared, and preserved. While some of the process of data curation is automated, much of the process involves extensive manual labor with multiple alerts (i.e., data queries) generated to study sites. TA3 will provide more complete automation of data queries and correction/completion of datasets, while also enabling more effective and seamless coordination between various trial sites.

TA3 Innovations & Deliverables

TA3 will develop innovative tools and processes that increase the use of automation for both curation and auditing to reduce costs, improve speed, and enhance efficiency for both activities. It is possible that the tools developed to extract and standardize data from EHRs (TA1, described above) will reduce the need for curation and auditing. Proposers are encouraged to outline compelling and innovative strategies for automatic remote auditing of clinical trials to ensure compliance with study protocols and regulatory requirements, enable spot checks, and confirm accurate data entry. Solution summaries will describe methods for maximizing the reduction of manual labor across auditing and curation processes. Proposers are encouraged to describe innovative tools that allow CROs and sites to collaborate and support clinical trials in a decentralized manner, using non-traditional sites (such as pharmacies, community centers, walk-in clinics, primary care facilities, the homes of study volunteers, and other non-medical facilities), thus enabling clinical trials to have an extended reach and increased access. Solution summaries will outline compelling and innovative strategies for enabling communication between sites, such as reporting issues and suggesting improvement**.** Taken together, TA3 will enable the inclusion of non-traditional sites into the network-of-networks by reducing manual labor, streamlining communication, and ensuring that sites adhere to protocol and regulatory requirements.

TA3 solution summaries must provide a technical plan describing how the proposer will develop or adapt a tool that meets aggressive performance metrics for the following objectives:

1. Automate audits to the extent possible, by providing tools to Lead Investigators to perform spot checks to ensure that data entry is accurate and reflects source documents, reducing the need for manual labor.
2. Automatic, remote auditing of clinical trials to ensure compliance with study protocols and regulatory requirements, reducing the need for costly and labor-intensive on-site audits.

3. Automatic matching of data elements from source documents (e.g., clinical records, demographic information, imaging reports) to data entered in study CRFs, ensuring data integrity and consistency.
4. Generate and resolve data integrity / quality queries automatically, alerting site personnel only when necessary.
5. Facilitate seamless coordination and communication between various trial sites and CROs / Trial Coordinators, enabling more effective management of decentralized trials and ensuring that all sites adhere to the same protocols and standards.
6. Enable sites to provide feedback to Lead Investigators to report issues and suggest improvements.
7. Supportability of Lead Investigators to monitor data collection across distributed sites and perform audits
8. Ensure the tool is developed with interoperability and modularity in mind so the individual tool can later be seamlessly integrated with other ACTR tools in a combined cloud platform.
9. Work with other performers to converge on common data standards and APIs that will enable interoperability across multiple CROs and clinical sites, even when they leverage different software solutions.

2.1.6 Initiative Structure

ACTR is a 5-year, 3-phase initiative that consists of three TAs and two types of Independent Verification & Validation (IV&V): Virtual Demonstrations and Real-World Evaluations. Each performer will be permitted to address any mix of TAs or sub-TAs that they choose, and ARPA-H will exercise the ability to partially fund solutions to ensure all TAs / sub-TAs have high-quality solutions. The deliverable from each of the TAs / sub-TAs will be a clinical trial tool that is interoperable with other tools developed in the ACTR initiative and generalizable to multiple clinical trial use-cases.

Throughout the ACTR effort, progress of performers will be continually compared against milestones (Figure 1), metrics (Figure 2), and by ACTR's IV&V functional assessors. ACTR will structure work across three phases as follows. In brief, potential performers will submit solution summaries only for Phase I of ACTR at this time. After evaluation of the solution summary documents, a subset of proposers will be invited to exhibit their capabilities. From those, performers will be selected for contracting per each full TA (i.e., TA1 and TA3) and/or for designated sub-TAs (i.e., TA2.1, TA2.2, and TA2.3). During Phase 1, performers will demonstrate the performance of their tools any time they are ready to do so after the award of the contracts, or by 48 weeks after that date. It is anticipated that from the Phase I performers per each TA and designated sub-TA, ARPA-H will downselect some of the performers to participate in Phases II and III of ACTR (subject to availability of funds).

Phase I: (**months 1-12**)

ACTR Tools Demonstration (weeks 1-48) – Performers will convene within 2 weeks of award to collaboratively define a reference architecture that adheres to all standards required by the ACTR initiative. This will involve the development of clear guidelines, APIs, and data exchange protocols that enable the smooth integration of the ACTR technologies with existing clinical trial management systems, electronic health records, and other relevant platforms. Performers will then develop their tools, and the tool performance will be evaluated as part of a virtual demonstration conducted by ARPA-H and IV&V partners to ensure that developed tools are

generalizable and interoperable. Performers will have access to real data sets provided by ARPA-H and/or other government partners while building and demonstrating their tools' capabilities. Tools are expected to function across multiple trial types (e.g., drug trial, observational trial, screening trial, etc.); use cases (e.g., pandemic preparedness, evaluation of novel clinical technologies / algorithms, screening and treatment of underserved populations, etc.); a variety of patient populations (rural, minorities, all ages, all manner of socio-demographic sub-populations, etc.); trial sizes (from a few thousand to 300K+); myriad data types (drug response data, participant survey data, observational data, imaging data, other lab data, algorithm output data, etc.); medical and clinical domains (e.g., cancer, diabetes, Alzheimer's disease) and different levels of user expertise (ranging from highly sophisticated clinicians, developers, and CROs to novice personnel at non-traditional trial sites). Tools are also expected to interoperate for seamless user experience and data sharing.

IV&V (weeks 49-52) – IV&V of tools and selection of those contractors that will proceed to Phase II.

Phase II: Integration and Real-World Evaluation (months 13-54) – Performers will configure and deploy tools at real-world trial sites and integrate them within a wide variety of clinical trial workflows for rigorous systems-level testing and iterative refinement. In Phase II, performers will work closely with Contract Research Organizations (CROs) and non-traditional clinical trial sites to ensure tools are functioning appropriately and gather user feedback. In Phase II, remaining performers will be expected to collaboratively integrate their tools into a shared cloud platform for modular and interoperable deployment in real-world settings.

Phase III: Evaluate Endpoints (months 55-60) – Performers will complete the refinement and integration of tool components within a clinical trial tool suite. Performers will collaborate with CROs to evaluate the trial endpoints and key metrics, in addition to measuring the return on investment that the tool suite would offer CROs in future trials. Performers will also work individually and/or in partnership with each other, CROs, and other government agencies to transition the tools to the commercial marketplace.

ACTR will structure Independent Verification and Validation (IV&V) for the initial phase as follows:

Virtual Demonstration (**weeks 1-48**) – The virtual demonstration is designed to assess TA tools as both individual components and as part of an integrated platform using real data in pre-defined datasets and simulations so that the tool performance can be assessed in a laboratory or pre-clinical trial environment. As described above, tools are expected to generalize across a range of use cases, accommodating the wide breadth of trial sites and data types that will make up ACTR's network-of-networks. To this end, the virtual demonstration will involve testing the performance and interoperability of the tools across several use-cases, which may align with several of the following categories: 1) Screening trials – large-scale studies designed to evaluate the effectiveness of a screening method in detecting a specific condition or disease across a geographically disperse population, 2) Prevention trials - evaluate the effectiveness of interventions in preventing the development of a specific disease or condition in healthy individuals or those at high risk, and 3) Pragmatic trials - evaluate the effectiveness of an intervention in real-world settings, with less stringent eligibility criteria and more flexible protocols compared to traditional randomized controlled trials (e.g., evaluating the efficacy of a vaccine in response to a pandemic pathogen). By the start of the effort, ARPA-H will identify an independent third party with experience running similar demonstrations or challenges to help conceptualize and judge the virtual demonstrations. In collaboration with the IV&V entity, ARPA-H will select

data sets that will be given to performers to demonstrate tool capabilities and performance against key metrics. The virtual demonstration IV&V will assess individual tool performance and interoperability with other tools culminating in a down-selection to one or more teams per tool. These remaining performers may have the opportunity to continue to Phase II and III in ACTR.

During Phase I, performers will work together to develop and/or refine common data standards and APIs that enable tools to interoperate across multiple CROs and clinical sites. Performers are expected to advance approaches that support multi-CRO clinical trials, even when each CRO and its associated sites use different software solutions. During Phase I, performers may develop common data standards, APIs, translators, reference implementations, implementation guides, architectural strategies, approaches to share schema, and code to enhance interoperability. Whenever possible, such artifacts should be developed with a commercial friendly open-source software license and shared across all performers, with the goal of creating a foundation for all clinical trial sites in the U.S. to interoperate in a seamless manner while minimizing the need for manual configuration. Later phases of ACTR (i.e., Phases II and III) are still under development. The continuation of ACTR beyond Phase I is dependent on a number of factors, e.g., successful outcome of Phase I, capability and suitability of potential performers, and availability of funding. It is anticipated that successful performers that complete Phase I will continue into the later phases of the initiative, subject to evaluation as described below.

Real-World Evaluation (months 13-60) – The real-world evaluations will occur throughout Phase II and III of ACTR and are designed to rigorously test and validate the tools and infrastructure developed within the TAs in clinical trial settings on a systems-level. In Phase I, tools will demonstrate they meet foundational requirements like data privacy, security and accuracy, whereas in Phase II, CROs will evaluate the refinement, integration, and deployment of clinical tools and infrastructure across two different real-world use cases. The specific details of the real-world evaluations will be announced six months prior to the start of Phase II. The two use cases will approach tool evaluation in different and complementary ways, leveraging unique clinical scenarios, patient populations, provider types, technical expertise of participants, and trial designs (e.g., efficiently extending screening, prevention, and pragmatic trial designs to non-traditional sites) to comprehensively evaluate the tools' performance and adaptability. Proposers will create dashboards that will monitor the relative performance of the tools and enable them to manage the decentralized trial sites throughout the real-world evaluations. In addition to evaluating the ACTR tools, CROs will innovate adaptations to other essential parts of the clinical trial infrastructure, including but not limited to the governance structure, cultural norms, and site-specific contracting mechanisms. Ultimately, the novel network-of-networks approach to clinical trials will require sociotechnical innovation that drives toward both novel software infrastructure as well as new business models to enable modular clinical trial networks to extend to where Americans live. At the conclusion of the real-world evaluations, TA performers and CROs will have data on the value that the tools provided to the clinical trials (e.g., return on investment via reduced labor, time, and trial resources), thereby enhancing their likelihood of successful commercial transition.

Real-World Evaluation 1: Decentralized trial with sophisticated users

91% of Americans live within a half hour of an imaging center, making them a key target for real-world evaluation of ACTR tools. Real-World Evaluation 1 will test the performance of TA1-3 tools in real clinical settings with more technically sophisticated users and a means of de-risking initial deployment and obtaining user feedback.

Real-World Evaluation 2: Decentralized trial with non-traditional sites

Technologies developed in TAs 1, 2, and 3 will be adapted to support clinical trials in less clinically sophisticated and non-traditional settings. By focusing on non-traditional sites like retail pharmacies, community centers, mobile health units, etc., Real-World Evaluation 2 is positioned to demonstrate massive benefit to historically underserved populations. Additionally, the Identification of Eligible Study Volunteers (TA2.1) and Individualized and Culturally Appropriate Consent Processes (TA2.2) tools are critical for reaching and engaging participants in community and rural settings. Additionally, the tools for Automatic Trial Data Prompting & Extraction (TA1) will be enhanced by deploying across a variety of sites and data sources. Finally, the novice users at non-traditional sites will help validate the user-friendliness and effectiveness of the tools.

2.1.7 Milestones & Metrics

Performers working on any Technical Area (TA1, TA2.1, TA2.2, TA2.3, TA3) must collaborate with those developing tools for other Technical Areas. This ensures that the final product from Phase 1 is functional, consistent, and compatible. This can be accomplished by, but is not limited to, aligning infrastructure, data, and communication standards; leveraging APIs and middleware for integration; maintaining data consistency and synchronization; implementing robust security protocols; ensuring performance and scalability; agile enhancements to the interoperability software through all phases and maintaining comprehensive documentation. A seamless integration of various tools is necessary for the real-world success of the ACTR program, and performers will be expected to work together to converge on common standards and APIs using an agile software development approach. Performers should leverage, adapt, and extend existing standards, such as those developed by Vulcan FHIR accelerator and other relevant HL7 accelerators, whenever possible. This holistic, team-based approach will result in a high-quality product, which will help accelerate the real-world implementation of clinical trials in Phase 2. Figure 1 highlights the timeline for a three-phase plan to develop, demonstrate, and integrate clinical trial tools, emphasizing virtual demonstrations in Phase I, deployment at real-world sites in Phase II, and endpoint evaluations in Phase III, with iterative refinement and stakeholder engagement throughout. Figure 2 highlights the metrics used to evaluate the tools developed.

Figure 1: Timeline and Milestones

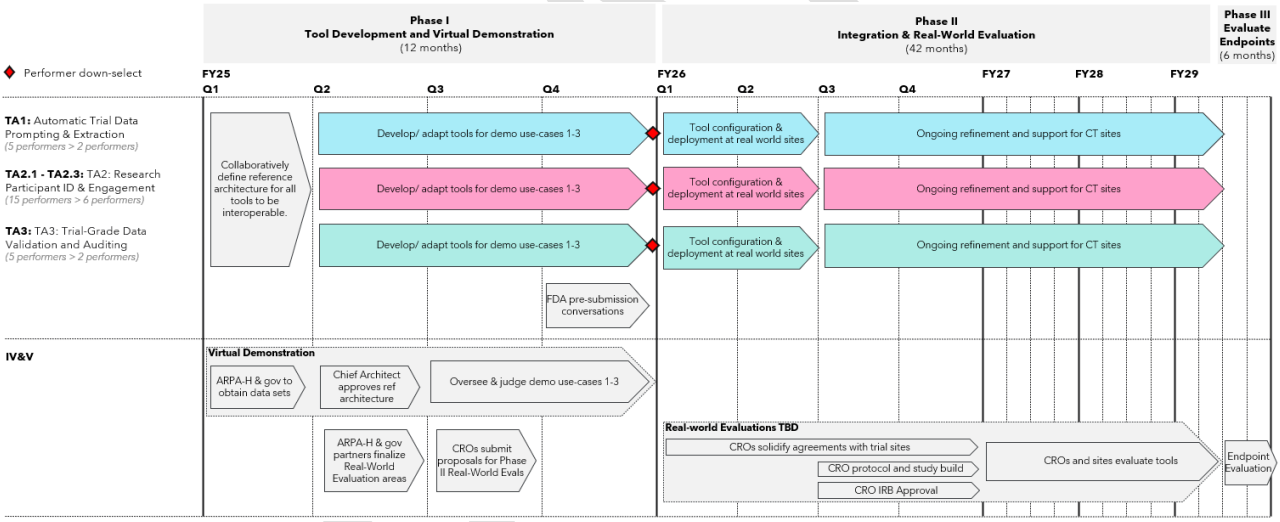

Figure 2: Metrics

TA		Metric	Phase I (0-12 mo.) Tool Development & Virtual Demonstration	Phase II (13-54 mo.) Integration & Real-World Evaluation	Phase III (55-60 mo.) Evaluate Endpoints
All		**Customer Experience / User Acceptance** (average Likert score [1-10 scale] for tool usability as judged by users)	≥ 7	≥ 8	≥ 9
		EHR & Platform interoperability: Number of platforms that ACTR tools are interoperable with (targets to be refined as clinical trials in Phase II & III are identified)	≥ 2	≥ 3 sufficient to extend to imaging centers and traditional sites	≥ 4 sufficient to extend to imaging centers, non-traditional sites, and traditional sites
		Number of trial sites: Number and type of sites where ACTR tools are deployed and undergoing iterative testing / refinement.	Software connections work across dozens of virtual sites (e.g., through virtual machines / simulations)	Dozens of real-world sites with sophisticated users	100's of real-world non-traditional sites w/ less sophisticated users (e.g., pharmacies, community centers, etc.)
TA1: Automatic Trial Data Prompting & Extraction	1	**Standardization of Protocol and CRFs:** percentage of data from different sources that can be successfully integrated into a unified dataset without errors	≥ 90%	≥ 95%	≥ 99%
	1	**Efficiency:** Relative reduction in time / effort required to fill out case report forms; adapt software / update protocols, etc.	≥ 50% (relative to historic averages)	≥ 85%	≥ 90%
	1	**Integration Variety:** Number of different EHR systems or modules/components plus number of EDCs with data integration capability	Set target	90% of target	100% of target
TA2: Research Participant ID & Engagement	2.1	**Accuracy of Automatic Clinical Trial Candidate Identification:** Proportion of automatically identified candidates that meet trial criteria.	≥ 80%	≥ 90%	≥ 95%
	2.2	**Speed of Enrollment:** % of weeks when site-specific enrollment targets are met. Targets established in pre-trial period.	Set target	60% over all sites	90% over all sites
	2.2	**Culturally Appropriate Consent:** Qualitative measure of proportion of participants that understand trial, consent, tools, and processes.	≥ 70%	≥ 90%	n/a
	2.3	**Participant Retention:** Proportion of participants that remain in trial.	Set target	≥ 90%	≥ 95%
TA3: Trial-Grade Data Validation & Auditing	3	**Data Curation:** Percent reduction in manual time spent reviewing data errors (e.g., accuracy, completeness, and consistency).	≥ 80%	≥ 90%	≥ 95%
	3	**Study Auditing:** Rate of detection of non-compliance through simulated insertion of regulatory and protocol noncompliance. Baseline defined as highest accuracy and established in first year.	Set baseline	≥ 90%	100%

2.1.8 Common Requirements & Opportunities for All Solution Summaries

Phase I Stipend Acknowledgement

Solution summaries should **acknowledge that work by selected Performers in Phase I will be eligible for a flat-rate stipend** of up to $412,000 or $494,000 for academic, non-profit, or federally qualified small businesses to be distributed on a monthly basis during the Phase I period of performance. Performer agreements will contain an option that the government may decide to exercise which extends the Performer agreement to cover Phase II and Phase III of ACTR.

Baseline Technical Requirements for Tools

Solution summaries for all TAs/sub-TAs must describe how the proposed tools currently meet or will be developed/adapted to achieve the following requirements where applicable and appropriate:

1. **Back-end data / software standards & architecture**
    a. Adhere to FDA Good Clinical Practice (GCP)[23] guidelines, which provide standards for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical trials.
    b. Security and Privacy
        i. Preferred solutions will integrate security and privacy considerations into the architecture from the outset.

[23] FDA GCP guidelines: https://www.fda.gov/science-research/clinical-trials-and-human-subject-protection/regulations-good-clinical-practice-and-clinical-trials

1. The National Institute of Standards and Technology (NIST) Special Publication (SP) 800-66r2[24] provides implementation guidance to assist with achieving HIPAA compliance.
2. The NIST SP 800-53[25] provides guidance on security and privacy controls that should be implemented to satisfy requirements to protect federal information and information systems.

ii. Must comply with HIPAA, when applicable:
1. For tools handling Protected Health Information (PHI) or those used by HIPAA-covered entities or their business associates, compliance with HIPAA is required.
2. For tools that do not directly handle identifiable patient data, strict HIPAA compliance may not always be required, but equivalent internal controls should be implemented.
3. Comply with Department of Health and Human Services (HHS) regulations for the protection of human subjects in research at 45 CFR 46[26] (Common Rule), which provides additional protections for human subjects involved in research conducted or supported by HHS and other federal agencies.

iii. Encrypt all Personally Identifiable Information (PII) and PHI in transit and at rest using AES 256, HTTPS, TLS, or equivalent.

iv. Preserve privacy on both structured and unstructured data for functions such as search and analysis without compromising patient confidentiality.

v. Should support data anonymization and de-identification features.

c. Data Sharing and Formatting Standards

i. Data exchanged across the ACTR platform should be structured and computable.

ii. Utilizing, configuring, and integrating existing data standards and capabilities is highly encouraged; for example, consider leveraging the following commonly used standards:
1. Clinical Data Interchange Standards Consortium (CDISC) Foundational Standards[27] for data representation in clinical research processes
2. Health Level Seven International (HL7) Fast Healthcare Interoperability Resources (FHIR)[28] and related Implementation Guides for standardized health care data exchange, as utilized by the Vulcan Accelerator Project (https://confluence.hl7.org/display/VA)
3. DICOM (for medical imaging if/where appropriate)
4. Pre-existing work on FHIR to CDISC mapping[29]
5. Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM)[30] for structured observational data and analyses

[24] NIST SP 800-66r2: https://nvlpubs.nist.gov/nistpubs/SpecialPublications/NIST.SP.800-66r2.pdf
[25] NiST SP 800-53r5: https://nvlpubs.nist.gov/nistpubs/SpecialPublications/NIST.SP.800-53r5.pdf
[26] 45 CRF 46: https://www.hhs.gov/ohrp/regulations-and-policy/regulations/45-cfr-46/index.html
[27] CDISC: https://www.cdisc.org/standards/foundational
[28] HL7 FHIR: https://www.hl7.org/fhir/
[29] CDISC Mapping: https://www.cdisc.org/standards/real-world-data/fhir-cdisc-joint-mapping-implementation-guide-v1-0
[30] OMOP CDM: https://www.ohdsi.org/data-standardization/the-common-data-%20model/

6. Representational State Transfer (REST) Application Programming Interfaces (API) and JavaScript Object Notation (JSON) for web-based data exchange

d. Access Controls
   i. Must have authentication and authorization mechanisms to allow access to authorized users only.
   ii. Should support access for participant caregivers, patient advocates, and/or family members, when needed.
   iii. Upon completion of data collection, implement a database lock to prevent any upstream changes, preserving the integrity of the collected data.

e. Auditing and Monitoring
   i. Include audit trail features to protect patient data and ensure compliance with FDA and HIPAA regulations.
   ii. Include continuous monitoring and auditing features to ensure ongoing compliance, security, and integrity.

f. Data Integrity
   i. Must comply with FDA guidelines 21 CFR Part 11[31], under which FDA considers electronic systems, electronic records, and electronic signatures to be trustworthy and reliable.
      1. Incorporate necessary security features including encryption, access controls (21 CFR 11.10(d)), and audit trail functionalities to protect patient data.
   ii. Implement checks and balances to ensure data integrity across different stages of data processing.
   iii. Manage integrity of information received from disparate electronic systems.
   iv. Maintain metadata and data provenance information.

g. Interoperability
   i. Compatible with a common data infrastructure that will underpin the network-of-networks approach of ACTR, which will be jointly defined across performers in Phase I.
   ii. Modular, reusable, and interoperable with other tools being developed in ACTR for seamless data sharing and user experience.
   iii. Interoperable with existing resources / infrastructure at non-traditional trial sites.

h. Scalability
   i. Support multiple deployment models, such as local deployment within health system, centralized deployment within cloud environment for use by multiple health systems, hybrid models, etc.
   ii. Ensure the infrastructure can handle increasing data loads and expanding user bases, and tools are scalable to distributed and decentralized populations in support of decentralized trials (e.g., at a minimum, up to 1000s of large clinical trials at 1000+ sites, and 300K+ participants).

2. Requirements for tools to accommodate diverse use-cases *(refer to metrics in Figure 2)*

[31] Code of Federal Regulations Title 21 Part 11: https://www.ecfr.gov/current/title-21/chapter-I/subchapter-A/part-11

a. Clinical Trial Considerations
    i. Applicable to multiple clinical trial types (e.g., drug trial, observational trial, screening trial, etc.)
    ii. Applicable to multiple clinical trial use cases (e.g., pandemic preparedness, evaluation of novel clinical technologies / algorithms, screening and treatment of underserved populations, etc.).
    iii. Allow for the customization of different workflows and protocols to enable the tool to adapt to different clinical trial designs and methodologies.
    iv. Compatible with clinical trials using reusable trial protocols and components established by ACTR
b. Patient and Participant Considerations
    i. Applicable for a wide variety of patient populations (rural, minorities, all ages, all manner of socio-demographic sub-populations, etc.) including being adaptable to different cultural contexts, languages, and health literacy levels for participant-facing materials and user interfaces.
    ii. Identification tools for potential study volunteers should be user-friendly and accessible to non-traditional sites, including those serving rural and underserved populations, different socio-economic backgrounds, various cultural and ethnic groups, and individuals with different educational levels and English-language proficiencies.
    iii. Allow configurability to address unique privacy considerations – for example, adolescent medicine restricts parental access to patient portals to protect the adolescent's privacy, complicating parental involvement in healthcare management.
c. Data Handling and Integration
    I. Able to process, exchange, and integrate diverse data types and formats (drug response data, participant survey data, observational data, imaging data, other lab data, algorithm output data, etc.).
    II. Facilitate collaboration and integration across multiple sites and stakeholders, including non-traditional locations such as retail pharmacies and mobile health units, while also ensuring compatibility with various healthcare data systems and standards (e.g., HL7 FHIR).
    III. Enable local data storage on devices when offline, and automatically synchronize this data with the central database once a secure internet connection is re-established, ensuring continuous operation in remote areas.
    IV. Consider the specific laws and internal policies of the states or countries and health systems involved to determine the impact on the clinical trial data management strategy. Data localization regulations can impact clinical trials by imposing restrictions on where data can be stored, processed, and transferred, potentially complicating multi-site studies.
d. User Experience and Accessibility

i. Able to accommodate different users (ranging from highly sophisticated clinicians, developers, and clinical research organizations (CROs) to novice personnel at non-traditional trial sites).
ii. Allow for the creation of tailored user interfaces for different user groups to enhance usability and minimize the learning curve while accommodating users with varying levels of technical expertise.
iii. Implement features that comply with accessibility standards (e.g., Web Content Accessibility Guidelines)[32] to ensure usability for individuals with disabilities.

e. Remote and Real Time Capabilities
i. Tools should facilitate remote participation, ensuring data collection, monitoring, and communication between participants and researchers, regardless of geographic location.
ii. Tools should incorporate advanced technologies such as wearable devices, mobile health apps, and electronic health records to gather comprehensive, real-time health data and enhance patient engagement and adherence.

Collaboration and Data Sharing

The ARPA-H ACTR Initiative will be developed by several performers selected through this announcement. **It is expected that all performers will interact and work collaboratively with other performers in developing the methods, technologies, and tools using open, timely, and effective communication, information exchange, and reporting.** Performers across all partner organizations will attend common meetings and technical exchanges to advance relevant technologies, bridge across data siloes, and move toward a common care delivery platform across numerous clinical use cases.

To facilitate the open exchange of information described above, **performers will have an Associate Performer Agreement (APA) language included in their award.** Each performer will work with other ACTR performers to develop an APA that specifies the types of information that will be freely shared across performer teams. The open exchange of scientific information will be critical in advancing the ACTR objectives. The APA will establish a common understanding of expectations to guide the open exchange of ideas and establish a collaborative foundation for ACTR. Each performer will work with other performers as described in the Collaboration Requirements (Figure 3).

Figure 3: Collaboration Requirements

TA	Collaboration Expectations
All funded participants	Throughout the effort, all performers will work with Independent Verification and Validation (IV&V) teams established by ARPA-H. IV&V expectations are described in Section 1.3.5. All TA performers, in collaboration with ARPA-H and the IV&V team, will align on technical standards for data storage and sharing, including common data standards, formats,

[32] Section 508: https://www.section508.gov/

	specifications and APIs to enable consistency and accessibility across all performers while preserving data provenance and patient privacy.
Tool Developers (TAs 1-3)	**With all TAs:** In Phase I, tool developers should collaborate to define a reference architecture to ensure tool interoperability during and following the ACTR initiative. Tool developers may collaborate during Phase I, if desired, to ensure and/or enhance interoperability and other functionalities of their tools. In Phase II, remaining tool developers will collaborate to integrate, configure, and deploy their technologies in real-world evaluation use cases at participating clinical trial sites as part of the second IV&V.
	With CROs: During Phase II and III, tool developers should collaborate with CROs to implement the ACTR suite of tools across trial sites. Tool developers are expected to be responsive to feedback provided by CROs and iteratively improve tool capabilities, performance, and user experience. CROs will collect data to evaluate the tools, including input from personnel at their sites, as part of the real-world evaluation.
	With clinical trial sites: In Phase II, tool developers should collaborate with clinical trials sites to install integrated tools with cooperation from site personnel and the CRO that is overseeing each. Additionally, tool developers are expected to be responsive to feedback provided by clinical trial sites to iteratively improve tool functionality and user experience.
	With IV&V: In Phase I, tool developers should collaborate with ARPA-H and a third-party IV&V as part of a Virtual Demonstration. Data sets and materials will be provided to tool developers to demonstrate tool capabilities prior to a down-select. During Phase II and III, tool developers should collaborate with the IV&V partners, which will include CROs, to assess and refine ACTR tools during Real-World Evaluations. CROs will develop dashboards, designed for specific clinical trial use cases, for data collection and analysis.

Open Software Standards

Performers will be expected to adhere to all relevant Government laws and policies applicable to data and information systems and technologies, including but not limited to:

- Common IT Security Configurations
- Federal information technology directives and policies
- Section 508 of the Rehabilitation Act of 1973 (29 USC 794d) as amended by P.L. 105-220 under Title IV (Rehabilitation Act Amendments of 1998)
- National Institute of Standards and Technology (NIST) Risk Management Framework Special Publications

A key goal of the project is to enable multi-CRO clinical trials that extend to non-traditional sites, regardless of the software used to facilitate the trials. Interoperable data standards and APIs will play a critical role in establishing multi-CRO interoperability, regardless of which software solutions the CROs use. Throughout the ACTR initiative, performers may work together to develop common data standards, APIs, translators, reference implementations, implementation guides, architectural strategies, approaches to share schema, and code to enhance interoperability; and these interoperability-enhancing artifacts should be developed with a commercial friendly open-source software license or unlimited rights. They should also be shared across all performers, with the goal of creating a foundation for all clinical trial sites in the U.S. to interoperate in a seamless manner while minimizing the need for manual configuration. Open-source code and artifacts

are highly encouraged to use permissive, business-friendly open-source licenses such as CC-BY, BSD, MIT, Apache 2.0 or similar. Approaches that inhibit this objective are not desired and would adversely affect the ACTR goals and objectives.

All data, protocols, and software that is developed, used, or extended during ACTR initiative must be adherent to relevant standards established or endorsed by ONC (e.g., HL7, FHIR, DICOM, LOINC, SNOMED CT, USCDI, and USCDI+). It is expected that all performers will work together to converge on standards and APIs to ensure interoperability across prototype capabilities. All performers are expected to follow agile software development processes. Whenever an existing standard is available that meets technical needs of the effort, performers must use the existing standard instead of creating their own. In cases where an existing standard provides only partial functionality, performers should extend the existing standard in a fully backwards compatible manner and create the documentation needed for ONC to evaluate extensions for inclusion in the national standard.

All Application Programming Interfaces (APIs) developed for ACTR must be founded on open standards and models such as REST, JSON, JSON-LD and utilize standard data models and ontologies if available. All data elements and structures in API calls must be mapped to a data dictionary that references the standards.

Commercial Transition Support

Proposers who are selected for an ARPA-H award may apply for a team of non-government advisors known as Entrepreneurs in Residence (EIR) / Experts in Residence (XIR). In coordination with the PM, the EIR/XIR will provide commercial transition support to the awardee. The goal is to offer complementary capabilities to the team; hence, the extent of the work is flexible. Examples of tasks may include cost modeling, end-user engagement, market analysis and mapping, competitive analysis, techno- economic analysis, manufacturing and scale-up strategy, intellectual property (IP) securement strategy, and financial plan creation. All commercialization and transition activities should align to the technology's stage of maturity. EIRs/XIRs will work closely with ARPA-H's Project Accelerator Transition Innovation Office (PATIO) team to leverage its extensive network of U.S. investors, strategic partners, and mentors.

Participation in the ACTR effort is voluntary. Performers are not expected to form a new company or leave their current research positions to pursue transition. Instead during the effort, performers should identify appropriate partners for enabling transition.

Accessibility Requirements

ARPA-H is committed to creating access to health care irrespective of race, ethnicity, gender/gender identify, sexual orientation, disability, geography, employment, insurance, and socioeconomic status. Accessibility considerations will be monitored throughout the effort, including review of milestone reports, deliverables and evaluations to ensure the prioritization of accessibility.

All proposers must articulate how they will incorporate accessibility considerations. Solution Summaries covering TA1 must describe how the outlined tools will catalyze the inclusion of non-traditional sites into a clinical trial network-of-networks by reducing barriers to entry, logistical challenges, cost, and time. Solution summaries covering TA2.1-TA2.3 must detail how their innovations will ensure that all

participants, regardless of their background, can fully understand and engage with the clinical trial process, thus fostering a sense of trust, transparency, and partnership. Solution summaries covering TA3 must detail how their innovations and deliverables will consider decentralized auditing and curation for different stakeholders, including clinicians, trial participants, and CROs.

Performers involved in the handling of personalized and/or identified demographics or health data must ensure appropriate privacy and security standards are met. All proposers should outline accessibility goals, potential risks, potential ramifications of not meeting accessibility goals and risk mitigation strategies.

3. Evaluation Methodology

This Request for Solutions (RFS) is a competitive solicitation seeking solutions for innovative technologies that address the topic areas under Section 2. Each Solution Summary will be evaluated on its own merit. **ARPA-H is under no obligation to respond to every submission, proceed with any Solution Summary/Exhibition, or select any specific number of Solution Summaries/Exhibitions in each technical area.** ARPA-H may also elect to fund one, several, or none of the proposed approaches to a given technical area.

Based on the evaluation of the solution summaries, some proposers will be invited to exhibit their proposed products and capabilities. These capabilities may include specific approaches to requirements analysis and tool design, data collection framework setup, data element standardization, dataset development and extraction, real-world data integration and decentralized trial adaptation, system testing and feedback, and final tool deployment, all relevant to the ACTR initiative. Additionally, based on the evaluation of the exhibitions, some proposers will be selected to proceed to Collaboration and Negotiations.

During the evaluation process, submissions may be handled by support contractors for administrative purposes and/or to assist with technical evaluation. All support contractors performing this role are expressly prohibited from performing ARPA-H-sponsored technical research and are bound by appropriate Non-Disclosure Agreements (NDAs).

3.1 Evaluation Process

3.1.1 Solution Summary

ARPA-H will evaluate the submitted Solution Summaries based on the evaluation criteria below. The Solution Summaries must clearly align to the RFS technical areas (Section 2) and comply with all requirements detailed in this RFS. Some submissions will be invited to the exhibition of their capabilities. **Due to expected volume of submissions, proposers will only be notified about whether they advance to the exhibition of capabilities phase. Proposers WILL NOT RECEIVE FEEDBACK on their individual submissions**. As such, a proposer's Solution Summary may be evaluated to be of merit, but not invited to exhibit their capabilities.

3.1.2 Exhibition of Capabilities

During the virtual exhibition of capabilities sessions, the proposing team will present their capabilities in 30 minutes to the ARPA-H team, followed by a 15-minute Question and Answer (Q&A) session which could possibly be recorded to allow for later review. The virtual sessions will allow ARPA-H to evaluate the submissions quickly and efficiently. As needed, ARPA-H reserves the right to ask proposers for additional information. ARPA-H will evaluate the capability exhibitions based on the stated evaluation criteria in Section 3.2. **Due to the expected volume of submissions, proposers will be notified about whether they advance**

This is a DRAFT Program Solicitation. This is not an invitation for solution summaries or proposals. Any such response will be disregarded. ARPA-H will not comment nor provide feedback on questions related to proposal technical approaches. Questions and Comments should be directed to arpa-h-cx-hub-contracts@ati.org.
to Invitation for Collaboration & Negotiation (IC&N). Proposers WILL NOT RECEIVE FEEDBACK on their individual submission.

The Government will not pay proposers for costs associated with solution summaries or exhibitions of capabilities, unless otherwise stipulated.

3.1.3 Invitation for Collaboration & Negotiation (IC&N)
After evaluating all the solution summaries and the exhibitions of capabilities of those selected, the ARPA-H team will select proposers to proceed to the IC&N Phase. Proposers will be notified after their exhibition of capabilities if they are selected or not selected to move onto IC&N. ARPA-H reserves the right to limit the number of proposers invited to IC&N. As such, a proposer's solution summary and exhibition of capabilities may be evaluated to be of merit, but not invited to IC&N. Those not invited to IC&N Phase will be notified via email. No additional feedback will be provided.

The selected proposers will work with the PL or designated technical team to collaboratively develop the following items:

1. Statement of Work (SOW) for all phases of the program
2. Technical Milestones for all phases of the program
3. Project Timeline covering the entire program
4. If Applicable - Government Furnished Property (GFP) / Government Furnished Information (GFI)
5. Intellectual Property
6. Cost estimates for phases II and III of the ACTR initiative

The Government will not pay proposers for costs associated with IC&N (e.g., solution summary or capability exhibitions, negotiations), unless otherwise stipulated.

After the IC&N Phase is completed, an award will be issued to the selected proposer. Awards will be made in the form of Technical Direction Letters (TDLs) from the Agreements Officer (AO) to the Customer Experience (CX) Hub CMF. The TDL triggers the CMF to issue a subaward to the selected proposer. Each TDL will incorporate the collaborative SOW (e.g., milestones, timeline, GFP/GFI, IP, costs) and all TDLs will be governed by the CMF's Base OT Agreement, unless otherwise noted in the TDLs.

Note 1: Templates will be provided to those selected for IC&N.

Note 2: It is required to have a www.SAM.gov Unique Entity Identifier (UEI) or CAGE Code to apply.

3.2 Evaluation Criteria

ARPA-H will use the same evaluation criteria to evaluate the Solution Summaries and Exhibitions of Capabilities. ARPA-H will use the criteria to determine which submissions will be invited to move to the next phase of the evaluation process.

For this solicitation, technical merit takes precedence in the evaluation process and will be assessed first. Solution Summaries and Exhibitions of Capabilities lacking technical merit will not be evaluated further. Solution Summaries and Exhibitions of Capabilities showing technical merit will be evaluated based on the remaining criteria listed below. Solution Summaries and Exhibitions of Capabilities will be evaluated on the basis of the merit of the proposed concept in addressing the Technical Areas. If an Organizational Conflict of Interest (OCI) presents itself during the Evaluation, ARPA-H will assess the OCI and decide if the potential OCI can be avoided or mitigated. If a potential OCI cannot be avoided or mitigated, ARPA-H will

remove the proposer from further consideration. All support contractors (e.g., XIR/EIR, SETA, etc.) supporting ARPA-H are expressly prohibited from performing ARPA-H-sponsored technical research and are bound by appropriate non-disclosure agreements (NDAs).

ARPA-H will use the following criteria to evaluate Solution Summaries and Exhibitions of Capabilities:

1. **Technical Merit:** The proposed solution identifies clear, measurable goals that have a reasonable chance of meeting the topic objectives. The potential of the proposed solution for technological innovation – whether the end-product or technology proposed would offer significant advantages over existing approaches, methodologies, instrumentation, or interventions currently used in research or clinical practice. Further, the proposed solution should align with the ARPA-H mission.

2. **Technological Innovation:** The potential of the proposed methodology for technological innovation, including whether the end product or technology proposed would offer significant advantages over existing approaches, methodologies, instrumentation, or interventions currently utilized in research or clinical practice, will be evaluated.

3. **User Experience:** The proposed solution contemplates the end user, first by understanding for whom the solution solves. For example, who will use this? Second, the solution meets the needs of the end user, whether patients, providers, health systems, or payers. For example, how would this solution fit inside the current clinical workflow? Or, how will this be accessible to users in all geographies, and at an affordable cost?

4. **Commercial Viability:** The potential of the proposed solution for commercial application and proposed methods of overcoming potential barriers to entry in the competitive market landscape include factors like whether there is an existing market for the solution, the size of the market, viable regulatory pathway, reimbursement, pricing strategy, competitive landscape, cost of production, business model, and revenue potential.

5. **Proposer's Capabilities and Related Experience:** The qualifications of the proposed Principal Investigators, Project Directors, supporting staff, and consultants, and the appropriateness of the leadership approach (including the designated roles and responsibilities, governance, and organizational structure) will be evaluated. The proposer's previous experience in software implementation for similar applications will be taken into account. Prior similar efforts demonstrate an ability to deliver products that meet technical performance standards within the proposed budget and schedule. The proposal must illustrate the team's capability to effectively manage cost and schedule considerations. Completed and ongoing efforts in similar areas, including collaborations with other government entities, should be fully described.

4. Submission Instructions

It is important to read and follow the "Solution Summary" preparation instructions carefully, which are outlined below. Pay special attention to the requirements concerning Human Subjects if your project encompasses that item (see Human Subjects Research).

If invited to exhibit technical capabilities, proposers must apply to become a Customer Experience (CX) Hub Spoke, if they haven't already. If selected for award, proposers must have their spoke approval and UEI to receive award.

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Solution Summaries will be submitted through the BIDS portal where Advanced Technology International (ATI) serves as the BIDS system administrator. All proprietary submission information will be protected. A proposer's submission under this RFS indicates concurrence with the aforementioned responsibilities.

Proposer teams may only submit one Solution Summary/Exhibition of Capabilities per tool in each technical area but may submit to all technical areas. The Team can be any mix of eligible institutions/organizations and can be part of multiple Solution Summaries/Exhibition of Capabilities.

For purposes of the salary limitation, the terms "direct salary," "salary," and "institutional base salary," have the same meaning and are collectively referred to as "direct salary". An individual's direct salary is the annual compensation for their direct effort (costs) under the CX Hub Agreement. Direct salary excludes any income that an individual may be permitted to earn outside of the CX Hub Agreement. Direct salary also excludes fringe benefits, overhead, and general and administrative expenses (also referred to as indirect costs or facilities and administrative costs). The salary rate limitation does not restrict the salary that an organization (i.e., ATI) may pay an individual working under an ARPA-H agreement; it merely limits the portion of that salary that may be paid with appropriated funds.

The salary rate limitation applies to all subawards, subcontracts, and subagreements.

FFRDCs and U.S. Government Entities are not eligible to propose to this requirement in any capacity, including as subawardees.

4.1 Basic Information:

The following information fields are required for successful submission:

- Solution Summary Title
- Technical Area #
- Organization Name
- List prior work in related field
- Organization Address
- Organization's UEI
- Website
- Point of Contact Name
- Point of Contact Email Address
- Point of Contact Phone Number
- Key personnel (including core competencies and levels of effort)
- Other Team Members (subawardees and consultants) if any

Note: Non-U.S. entities may participate to the extent that such participants comply with any necessary nondisclosure agreements, security regulations, export control laws, and other governing statutes applicable under the circumstances. However, non-US entities are encouraged to collaborate with domestic U.S. entities. In no case will awards be made to entities organized under the laws of a covered foreign country (as defined in section 119C of the National Security Act of 1947 (50 U.S.C. § 3059)) or entities suspended or debarred from business with the Government.

4.2 Solution Summary:

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A four-page maximum Solution Summary, using a minimum 12-point font, and with minimum 0.5" margins on all sides, should be submitted in a PDF format to the ARPA-H Customer Experience Hub ACTR Website listed on the RFS cover page (see Solution Summary Template for more details). Attachments shall not be included. Smaller sans serif fonts may be used for figures, tables, and charts.

The Solution Summary should address why the proposed idea is relevant to the proposed technical area in Advancing Clinical Trials Readiness. The Solution Summary should demonstrate the technical merit, user experience, commercial viability, and team qualifications.

- What health problem are you trying to solve? (Clearly state the objectives of your proposed solution or approach. Include the TA being addressed and the desired outcome.)
- How is it done today, and what are the limits of current practice? (Provide a summary of the current state of the art or existing practices and explain the challenges or gaps your solution addresses.)
- What is new in your approach, and why do you think it will succeed? (Describe the innovative aspects of your approach and provide a rationale for its success based on past performance, data, or research.)
- Who cares? (Identify the stakeholders or end-users who will benefit from your solution and describe how it meets their needs.)
- If you are successful, what difference will it make? (Outline the expected impact of your solution, including tangible and intangible benefits.)
- Team qualifications
- R&D timeline—what you can accomplish in the agreed upon project timelines?

Note 1: Any references can be added as an appendix and will not count towards 4-page maximum.

4.3 Exhibition of Capabilities:

Those invited to participate to provide a virtual exhibition of their capabilities should be prepared to show how their tool or tools perform, answer questions about their performance, and/or explain how they will be adapted to accomplish the tasks outlined for the TA or TAs for which they are proposing to participate in Phase 1 of ACTR.

For TA1: Automatic Trial Data Prompting & Extraction, potential performers must address the following issues-

a) Standardization of Protocol and Case Report Forms (CRFs). How accurately does their tool extract data from non-structured source documents without errors and standardize it using a widely used ontology?
b) Efficiency. When given source documents, how quickly can their tool extract data from source documents?
c) Integration Variety. What types of source documents have their tool been used on previously or can it be expected to perform accurately and quickly to extract and standardize data?

For TA2: Research Participant ID and Engagement, potential performers must address the following issues:

TA2.1:

a) Accuracy of automatic clinical trial candidate identification. How accurately can potential clinical trial volunteers be identified from electronic health records?
b) Speed of Identification. How quickly can their tool identify potential clinical trial volunteers from electronic health records?

TA2.2:

a) Culturally Appropriate Consent. How well does their tool create culturally appropriate consent documents from clinical trial protocols, adapted to the usual concerns and language limitations of the most common subgroups of the US population?
b) Answering common trial queries: How well does their tool answer the most frequently asked questions of potential study volunteers?

TA2.3:

a) Participant Retention. How does their tool engage study volunteers after enrollment to reduce drop out of participants?

For TA3: Trial-Grade Data Validation & Auditing, potential performers must demonstrate how their tool will likely perform in two areas:

a) Data Curation. How does their tool clean data after extraction or entry to assure that it accurately reflects source document content? How fast is data cleaning?
b) Study Auditing. How accurately and quickly does their tool detect evidence of non-compliance with protocol requirements?

Note 2: Further instructions for the IC&N Phase will be provided to proposers once selected.