ADVANCING CLINICAL TRIAL READINESS (ACTR) INITIATIVE DESCRIPTION

About: The Advancing Clinical Trial Readiness (ACTR) Initiative is led by the ARPA-H Resilient Systems Office (RSO). ARPA-H RSO's focus area aims to create capabilities, develop mechanisms, and accelerate system integrations that enhance stability in the face of disruptive events. Resilient systems need to sustain themselves between crises – from the molecular to the societal – to better achieve outcomes that advance American health resilience at the population level. From software systems to manufacturing pipelines, biophysical systems to microbiomes, and patient communities to provider networks, reliability is key to maintaining high-quality care between and throughout crises such as pandemics, social disruption, cyberattacks, and financial disruptions.

Project Goals:
ARPA-H's Advancing Clinical Trial Readiness (ACTR) Initiative aims to establish a robust clinical trial infrastructure through the ARPA-H Customer Experience (CX) Hub and Spoke network. This project will advance, integrate, and extend clinical trial capabilities so that ARPA-H has efficient mechanisms to evaluate new technologies, therapies, and platforms. ARPA-H seeks novel clinical trial infrastructure designs that will enable rapid distribution of common clinical trial protocols across multiple geographic locations and sites in the case of a national emergency. Finally, ARPA-H seeks to characterize technical gaps in clinical trial capabilities to elucidate what future technological research & development will be needed to revolutionize clinical trials. Achieving these goals will result in capabilities that advance clinical trial readiness, demonstrating new tools and ways to rapidly execute more representative and distributed trials.

Many clinical trials study the impact of drugs, biologics, and devices, evaluating safety and efficacy of both novel and established interventions to address different conditions. The clinical trial process is essential to providing the evidence needed to secure regulatory approval, such that innovative, effective treatments can safely be prescribed by healthcare providers and get to patients, with randomized control trials (RCTs) long established as the gold standard for evaluators. Thousands of products are in the clinical trials R&D pipeline worldwide, with the U.S. accounting for the largest share. However, there are several issues with the current model. These include: (1) interoperability challenges among and across EHRs, electronic data capture (EDC) systems, and systems that manage clinical protocols; (2) resource-intensive enrollment processes that often result in non-diverse populations within studies; and (3) the potential for discrepancy in outcomes from running RCTs and running studies in messy, real-world settings.

The ACTR project will develop, evaluate, and integrate new tools and technologies to enable faster, less expensive, decentralized trials operating closer to/at points of care that are more representative across geography, age, gender, race, ethnicity, and socioeconomic status. Advances in AI/ML, along with increasingly adopted data standards (e.g., Fast Healthcare Interoperability Resources, or FHIR) to enable sharing of siloed and unharmonized healthcare data, hold promise for increasing the speed and representativeness, and decreasing cost, of clinical trials. The project will culminate with compelling demonstrations that show regulators, clinical investigator sites, evaluators, EHR vendors, and the

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pharmaceutical industry the feasibility and utility of rapid, representative, and decentralized trials with trustworthy data. This will be critical for successful public health responses, 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 inform regulatory science by demonstrating the amount and type of structure needed in trial design to generate actionable, generalizable evidence – e.g., how much "noise" can be tolerated, how much we can rely on EHRs to inform trial design, identify candidates, and integrate with Case Report Forms (CRFs), and how to better integrate trials at the point of care.

The project will be guided through a series of challenge problems and use cases. Some potential examples include the detection of adverse events during cancer treatment, the evaluation of drug-repurposing efforts using real-world data, the emergency distribution of clinical protocols to detect emergent pathogens, and the recruitment of hundreds of participants in a short period of time.

Technical task areas:
This effort is comprised of five technical task areas:

- Task 1: Enrollment and consent
- Task 2: Decentralized trials
- Task 3: Trial protocols and data collection
- Task 4: Test and evaluation
- Task 5: Transition

Task 1: Enrollment and consent
Today, identifying and enrolling patients into clinical trials is a time-intensive and expensive process and requires trained experts with both clinical trial and medical experience. Data systems – specifically EHR systems which contain patients' health records and EDC systems which hold all data related to clinical trials – were not originally intended to interoperate. The lack of shared data makes it difficult to cast a wide net for candidates and match them to clinical trial protocols. At this early stage for clinical trials, the data interoperability challenge is partly driven by privacy concerns; identifying trial candidates happens prior to obtaining patients' consent, and there is no tool to allow for easy identification, recruitment or outreach, and matching of candidates to trial protocols. Moreover, consent processes today are similarly manual and consent documents are frequently long, complicated and are not always capable of capturing patient preferences. They are not designed to ensure that candidates have concise, clear, and understandable information that allows them to determine whether a particular trial might be right for them, and to have a smooth and positive experience.

How might we accelerate patient enrollment in clinical trials and make it more representative of the U.S. population?

ARPA-H is soliciting innovative approaches that reduce the time it takes to identify and enroll clinical trial participants. We are particularly interested in novel computational approaches that reduce the manual effort required to recruit new participants and obtain electronic consent. We are interested in patient-centered consent processes that assist patients with enrolling into the right kinds of trials.

Evaluations may be based on patient satisfaction and comprehension in addition to the number of patients that have given their consent as well as the ease and simplicity of the process.

Task 2: Decentralized trials

RCTs have been designed to test a hypothesis in highly controlled circumstances, with study procedures performed according to specific protocol requirements, which may differ from their conduct in clinical care and separate collection of study data. This separation between clinical research and clinical practice is often the best way to ensure the quality of the study data, especially for purposes of regulatory submissions. But there are some drawbacks: participation in clinical research entails an extra burden for both healthcare providers (HCPs) and patients and trials tend to be carried out in well-resourced academic research centers or dedicated clinical research clinics. Furthermore, patients who have difficulty traveling to study sites because of transportation or other reasons are often from traditionally underrepresented groups and thus are further underrepresented in the study population, or even excluded all together. Lastly, study results may not be generalizable to either a representative (diverse) population, or to actual clinical practice.

How might we shift the conduct of clinical trials closer to clinical points of care for all Americans?

ARPA-H is interested in novel decentralized designs that integrate digital health technologies and expand to new kinds of study sites, such as retail and pharmacy entities with a strong, distributed community presence and reach rural and underserved areas. We expect that successful pragmatic study designs will be simple, align with clinical practice at the point of care, and integrate into existing workflows across locations and kinds of sites, identifying trainings and process improvements to ensure embeddedness and consistency. Additionally, we anticipate that performers may devise novel statistical methods and demonstrate ways to use real-world data from EHRs and other sources that allow sites and communities to formulate study questions and derive comparator arms.

Task 3: Trial protocols and data collection

Today, clinical data is often messy and cannot be easily linked across systems, complicating data use, re-use, and understanding. This creates a barrier to quickly distributing a common novel protocol to many sites and obtaining comparable data back.

How might we enable multi-directional and multi-level communication of data among clinical trial protocols and points of patient care?

ARPA-H is soliciting innovative approaches that automate data extraction and synchronization between EHRs and case report forms (CRFs), and evaluate and extend emerging standards, such as the FHIR Questionnaire and Questionnaire Response which enable the gathering of structured, hierarchical data necessary for analysis. We are interested in modular protocols (i.e., a set of “building blocks” that can be used to rapidly spin up many common clinical trial protocols).

We expect successful performers to develop a data platform and accompanying software tools to distribute, run, and collect data from a clinical trial protocol and leverage open standards – both data standards and Application Programming Interfaces (APIs) -- wherever possible. We are interested in novel AI/ML tools that support data cleaning and standardization, linkages, and analyses at the point of ascertainment to enable federated collaboration with deployable solutions across data

enclaves/commons. We are interested in clinical trial data and data collection mechanisms that simplify the process, cut out the noise, and streamline reporting processes, leaving only essential and meaningful data. We anticipate that performers will leverage privacy-preserving tools that de-identify data (without introducing bias that affects the analysis), preserve the FDA's ability to review source data, provide quality assurance on the de-identified data, protect information provenance, and enable widespread sharing of clinical trial study data to enable rapid re-analysis. Performer teams can anticipate an integrated demonstration to prove interoperability between EHRs and EDCs.

Task 4: Test and evaluation

Task 4 will include both user testing and challenge formulation for tasks 1-3. We anticipate that successful evaluators will form representative user groups and test the tools and methodologies at appropriate stages of development to evaluate use acceptance. We expect tests for patient and clinical acceptance, the development of software test harnesses, and stress tests across the sociotechnical system (i.e., the combination of human and software / hardware components).

Challenges might include: task 1 challenges for performers to evaluate how fast they can identify and enroll patients into clinical trials, while assuring ethical requirements are met, and patient satisfaction with new consent tools; task 2 challenges to assess novel statistical methods, success with distributing and integrating trial protocols at diverse sites, and calibration tests to gauge reliability of each site; and task 3 connectathons to test data integration between EHRs and EDCs.

With ACTR's emphasis on open standards, we expect that performers will conduct prototype demonstrations in response to devised challenges that evaluate the effectiveness of new standards and any refinements to existing standards. With novel solutions we hope to see novel ways to evaluate these new capabilities and technologies. We expect that successful evaluators will also determine the overall cost and benefit of integrating these new capabilities into the clinical trial system.

Task 5: Transition

As a proof-of-concept, we expect that task 5 performers will integrate the best-in-class capabilities into a well-functioning network through the CX hub and its spokes and use them to accelerate performance of real clinical trials for ARPA-H created capabilities. We anticipate that performers will integrate and test the tools developed under the first three tasks to speed enrollment, ease obtaining patient consent, increase representation, enable interoperability between data systems, and validate pragmatic trials. Authorizations to Operate (ATOs) (if needed), documentation and security checks to ensure operational use, implementation guides for emerging standards, and more, may accompany these new tools and capabilities as they are tested and refined.

To accelerate adoption, we seek to emphasize open standards, open-source implementations of those standards, and software tools. We expect ACTR to establish a set of standards that the CX Hub and Spoke network will adhere to in order to obtain funding for future ARPA-H clinical trials. The CX Hub will integrate these standards in a practical way through the implementation of standardized EDC platforms and eCRF leveraging the standards, including CDEs, developed by ACTR.

The goal is to develop technological breakthroughs, open-source tools, and standards that will change the current paradigm, and lead us to faster, cheaper, more generalizable, and more representative trials.

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Appendix A: Notional milestones

Table A below features early metrics, milestones, and objectives for TA1-4.

Table B contains notional challenges for TA5 that also indicate metrics to constitute the overall project-wide goals.

It is anticipated that these metrics and milestones will change and expand, particularly as government-led teams devise regular challenges and evaluations for Performers. Performers will share results and lessons learned at meetings with other Performers (see Appendix B for more information on expected meeting cadence).

TABLE A

TA	Metric	Baseline	Interim	Stretch
TA1	Speed of candidate identification	Establish baseline rate within 3 months (currently months to years)	Identify candidates within weeks	Identify candidates within days
TA1	Patient satisfaction with consenting tools and process	Establish baseline within 3 months	50% patient satisfaction	99% patient satisfaction
TA2	Integration into remote/retail site workflow	Integrate with 1 retail site	Integrate with 3 different types of retail sites	Integrate with 15 different types of retail and remote sites
TA3	Diversity of protocols	Establish baseline within 3 months	5 modular protocols	100 protocols supported through modular components
TA3	Connection with EHR and EDCs	Establish baseline within 3 months	Integration with 2 EHR vendors and 2 EDCs	Integration with 10 EHR vendors and 10 EDCs
TA4	Software assessment	Test software	Test software plus feedback from nurses & clinicians	Test feedback from real clinical trials
TA4	Evaluation methodology	Develop methodology	Publish methodology and assessment results	Execute methodology
TA4	Trial testing	Small scale mock trial	Large-scale mock trial	Real clinical trial(s)

TABLE B

Below are notional challenges for TA5 that will consist of actual clinical trials run through the Customer Experience Hub and Spoke network. As such, these are also the overall project-wide metrics.

Metric	Trial 1	Trial 2
# of institutions	10	100
Variety of institutions	Includes retail & home mgmt	Approach that allows 90% of Americans to participate from home or a location within 30 minutes from home
Types of protocols	Embedded/POC design	Interventional trial
Data sources	Add novel sensors and devices	Dozens of sensors and devices, apps, EHR workflows
Relationship to the patient population	Statistically representative sample	Statistically representative sample
Speed of enrollment	6 months	2 months

Appendix B: Requirements for participation

Associate Contractors Agreement (ACA)

Performers shall work together to develop an Associate Contractors Agreement (ACA) that specifies the types of information that will be freely shared across performer teams. The open exchange of scientific information, establishment of open standards, and sharing of data will be critical in advancing the state of the art required to achieve the ACTR objectives, and the ACA will establish a common understanding of expectations to guide the open exchange of ideas and establish a collaborative foundation for the ACTR project. Performers shall also work with other Performers to converge on open standards and APIs to ensure interoperability across prototypes, sites, and capabilities.

Performers shall sign Non-Disclosure Agreements as they will have access to data that will contain personally identifiable and/or business sensitive information.

Logistics and Reporting

Performers are expected to participate in logistics and reporting including the following:

- Regular status updates and technical meetings including:
  - Monthly status report meetings.
  - Quarterly project meetings with other Performers.
  - Bi-annual (twice per year) in-person project meetings, hackathons, and / or workshops to collaborate with other Performers.
- Use of standard project management and documentation applications as well as all applicable confidentiality, privacy, information security, and conflict of interest regulations and corresponding NIH and HHS policies.
- Monthly reporting of Subcontractor Cost, Schedule, and Performance (CSP).