Health Science Futures

Computational ADME Tox AnaLYsis for Safer Therapeutics (CATALYST)

Advanced Research Projects Agency for Health

ARPA-H-SOL-24-114

November 1, 2024

Table of Contents

1. Innovative Solutions Opening Solicitation Overview Information

Federal Agency Name:	Advanced Research Projects Agency for Health (ARPA-H)
Solicitation Title:	Computational ADME Tox AnaLYsis for Safer Therapeutics (CATALYST)
Announcement Type	Innovative Solutions Opening
Solicitation Number:	ARPA-H-SOL-24-114
ISO Contact:	Email: CATALYST@arpa-h.gov ATTN: ARPA-H-SOL-24-114
Solution Summary Submission Site:	https://solutions.arpa-h.gov/Submit-Solution/
Proposal Submission Site:	https://solutions.arpa-h.gov/Submit-Proposal/
Proposal Submission Questions:	https://solutions.arpa-h.gov/Ask-A-Question/
Dates:	All times listed herein are Eastern Time (ET)
Draft Release Date:	**October 16, 2024**
Release Date:	**November 1, 2024**
Questions & Answers (Q&A) Due Date:	Questions may be submitted to CATALYST@arpa-h.gov after the Release Date
Closing Date:	Solution Summaries: **November 25, 2024** at 5:00PM Proposals: **January 31, 2025** at 5:00PM
Anticipated Award:	Multiple awards are anticipated.
Types of Instruments That May Be Awarded:	Other Transaction (OT)
Participants/Proposers:	Universities, Non-Profit Organizations, Small Businesses and Other than Small Businesses
Any Cost Sharing:	Cost sharing may be encouraged or requested

2. Description of the Solicitation

2.1. Introduction

The goal of the CATALYST program is to develop AI/ML-enabled *in silico* human physiology modeling platforms for ADME-Tox simulation to replace the poorly predictive investigational new drug (IND) IND-enabling preclinical animal studies currently used. Drug research and development (R&D) rely on *in vivo* animal model testing as a preliminary step towards FDA approval. However, the current IND-enabling preclinical animal study paradigm is often an imprecise model for human physiology, leading to an inefficient and expensive drug development process that does not accurately predict human drug safety outcomes. By leveraging innovation within the areas of large-scale data mining, AI/ML predictive analytics, novel high-throughput living systems instrumentation, and simulation-based whole human physiology modeling, CATALYST will create new tools to replace the current approaches that fail to fully recreate human physiology.

CATALYST will develop validated and qualified *in silico* platforms for novel drug development. By demonstrating their acceptability for assessing drug safety, these platforms will create a new "Digital contract research organization (CRO)" sector that will transform the traditional CRO landscape. The program will focus on Good digital eXperimentation Practice (GXP) pharmacokinetics (including absorption, distribution, metabolism, and excretion) and pharmacodynamics (safety and toxicity) that correlate with various human physiological states. To promote adoption of these platforms upon validation, CATALYST will concurrently fund product sponsors to integrate them into novel drug First in Human (FIH) approval packages. The teaming between the methodology developers and product sponsors is required for CATALYST to be impactful in the drug development industry. Eliminating the need for animal testing in preclinical studies will substantially reduce drug development costs, time, and resources that often prevent drugs with smaller markets from progressing. By providing a more accurate model of human physiological diversity, the *in silico* modeling platforms have the potential to provide a more reliable estimate of drug efficacy. Improved precision of predictions through CATALYST's *in silico* platforms will result in increased success rates in human clinical trials, ultimately leading to faster, less expensive, and more effective drug development benefiting both patients and the broader healthcare ecosystem.

CATALYST envisions creating *in silico* platforms by incorporating human-relevant preclinical and clinical data while addressing current data gaps through: 1) innovations in data discovery and deep learning approaches to predict drug outcomes while unifying the diverse landscape of public and proprietary data, 2) developing novel living system approaches designed to emulate human physiology, and using these data innovations to 3) create human-based *in silico* physiology models for comprehensive preclinical assessments. Given CATALYST's focus on developing tools intended to be used in regulatory filings, methodologies developed within the program must meet good laboratory practice (GLP)-equivalent requirements. Further, these tools must be configured to replace studies that currently rely on higher-order mammals. Critical to the success of the program, CATALYST will require teaming between tool developers and product sponsors at program start to ensure the tools developed by CATALYST performers align to specific Contexts of Use (COU) in regulatory applications. The teaming between tool developers and product sponsors is required for the successful adoption and execution of these studies in Phase II of the program, in which ARPA-H will support the entirety of a candidate product's IND-enabling study package, including the replacement of existing methods with CATALYST developed tools. The successful completion of CATALYST will radically shift the current industry practice of preclinical and clinical studies to improve patient safety and access to novel therapeutics in clinical trials. CATALYST aims to transform first-in-human trial approval.

2.2. Program Overview

Current methods used in preclinical studies have demonstrated limited utility and are often confounding when compared to human data. The most common *in vitro* and *in vivo* preclinical testing methods lack relevance to human physiology, leading to high failure rates of drug candidates entering human clinical trials. For example, *in vitro* systems can fundamentally alter cell behavior due to incorrect cell microenvironments and are not yet currently developed for systems integration. Despite attempts to 'humanize' pre-clinical models, animal models are often poor predictors of human reactions to therapeutics due to interspecies differences in physiology and pathophysiology. Finally, the current computational models rely on allometric scaling and *in vitro* to *in vivo* extrapolation (IVIVE), which rely on the data generated from the animal models and *in vitro* models that fail to adequately represent humans (as mentioned above). These computational tools are generally not predictors of success across the drug development continuum and are not enabled for use in regulatory applications. This results in the present success rate of candidate therapeutics below 10%, with substantial failures during clinical trials and during post-licensure surveillance due to safety issues. Additionally, while recent changes in law and regulations have sought to ensure that clinical trials include diverse populations, barriers still exist to including pediatric, women of child-bearing age, pregnant women, and geriatric populations. Additional factors such as genetic and epigenetic variance, age, gender, metabolic rate, and disease background are too diverse to be accounted for in current clinical trial designs and preclinical animal studies. Innovation is needed to shift the paradigm and enable the ability to evaluate safety and efficacy in these populations preclinically.

In silico human physiology modeling platforms have the potential to revolutionize current preclinical and clinical studies. Successful implementation of *in silico* models will result in a substantial decrease in study costs and unnecessary animal usage, while significantly increasing the success rate of clinical trials through accurate prediction of the safety, toxicity, and availability of therapeutic candidates. They can also optimize FIH clinical trial design while informing other ways to optimize the success of a drug candidate.

CATALYST will revolutionize current preclinical and clinical study practices with the following deliverables:

- AI/ML-enabled *in silico* human physiology modeling platforms for ADME-Tox simulation, that replace IND-enabling preclinical animal studies. The platforms will be adaptable to create fit-for-use *in silico* models of various major organ systems in the human body.
- Living system tools that generate new human data, and fill human data gaps, for the development of *in silico* platforms for ADME-Tox simulation.
- Independently verified *in silico* platforms using existing or new human clinical data and comparable validated assays.
- Demonstrated predictive capabilities of the *in silico* platforms through regulatory qualification of these platforms, and proof-of-concept FIH approvals based on data generated by these platforms.

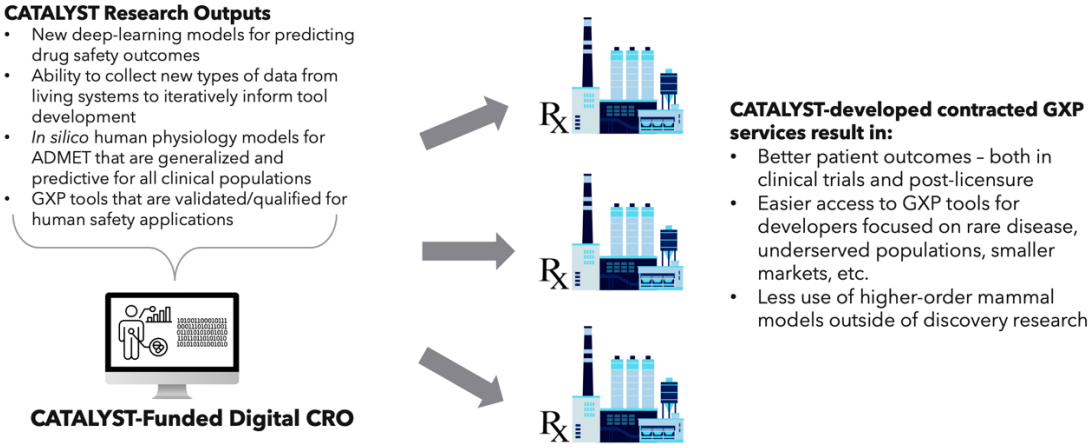

Figure 1. Examples of the inputs and outputs of the end state pursued by CATAYLST through the creation of "Digital CRO" that will add GXP in silico methods for use in regulatory applications in addition to current advancements in drug discovery and development further upstream.

Success in CATALYST will yield adopted methodologies that have been applied to IND-enabling studies, enhanced predictability of human outcomes in clinical trials, and a path towards digital clinical trials, more predictive Phase 0 studies, and drug candidates that have been evaluated in backgrounds that represent the population diversity of the United States. Technologies and methods developed in CATALYST will also create new market opportunities for "Digital CROs" to support more predictive regulatory science interaction that will enable easier clinical entry of drugs with smaller markets or that target underserved diseases and populations.

The ambitious goals of the CATALYST program align to broader U.S. government strategies such as the, White House Office of Science and Technology policy's AI Aspirations for Health (https://ai.gov/aspirations/). However, the approaches pursued here differ from other U.S. government research that seeks to improve new approach methodologies (or NAMs) in biomedical R&D broadly, such as the NIH Common Fund Complement-ARIE (Complement Animal Research In Experimentation) effort. CATALYST will pursue in-depth development of a predictive and regulatory-aligned platform with detailed requirements to be pursued in the first phase of CATALYST, and the CATALYST program will exclude generalized NAM approaches to be more broadly applied to biomedical R&D. CATALYST teams will then demonstrate COU for drug development and adoption of technologies to advance pharmaceutical candidates into FIH clinical trial approval in Phase II of the 5-year program.

2.3. Program Structure and Technical Approach

2.3.1. Program Structure

CATALYST is divided into two phases:

Phase I: Accelerated Technology Development and Method Qualification (36 months) – In Phase I, teams will focus on developing technologies that meet the *in silico* predictive goals of CATALYST. This will be through the pursuit of three technical areas (see Section 2.3.2) led by teams built around the "Digital CRO" concept. At the end of Phase I, teams will submit their technologies into novel drug development tool qualification pipelines that will facilitate their use in IND-enabling studies. Proposing teams must also include a Product Sponsor (see Section 2.3.2) will advise on COU and provide additional support to platform development in Phase I. Upon successful Phase I completion, Product Sponsors will lead the

adoption of these platform methodologies in Phase II, as described below;

Phase II: COU Concept Demonstration and Methodology Adoption – In Phase II, the team composition will shift towards Product Sponsor leadership, in which drug developers will pursue regulatory filings that include the *in silico* platform developed in Phase I in place of traditional, less predictive methods that rely on higher-order mammal experimentation. CATALYST will support IND-enabling experiments to include the replacement of traditional methods and any additional data generation needed to support regulatory approval towards human clinical trials. Successful execution in Phase II of the program will demonstrate the potential of the *in silico* platform methodologies developed in Phase I and the reality of the "Digital CRO" concept supporting more accurate, cheaper, faster, and most importantly safer outcomes for clinical trial participants and users of licensed products.

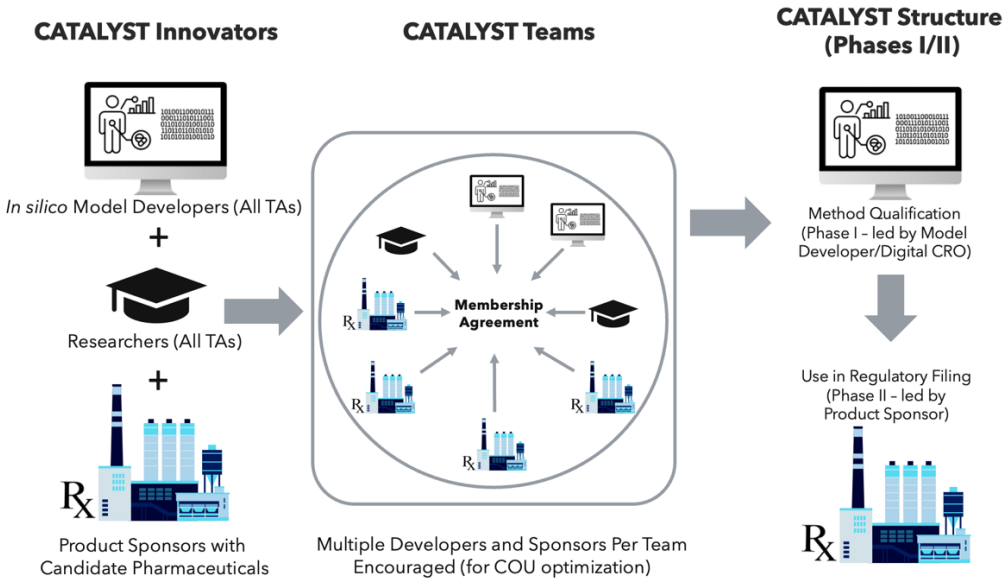

Figure 2. CATALYST Program Overview. The in silico Method Developers and Researchers (Left) include all three TAs. The teaming (Center) requires all facilitators as team members, and the Phase I and II of CATALYST (Right) are led by method developers and product sponsors, respectively.

The Other Transaction (OT) agreement is anticipated to be utilized in a team structure, with "team" meaning a group of organizations working together to accomplish a common goal, with members sharing resources, knowledge, and expertise, as opposed to a more traditional prime/subperformer structure. Although one member may lead the team and serve as its authorized agent for administrative purposes such as executing documents or receiving payment on behalf of the team, each member must be bound to the team membership agreement, must be a party to the resultant OT award with ARPA-H, and each member must perform substantive technical work as part of the team. By employing this teaming approach to the CATALYST execution, proposing teams will pursue technology development, proof-of-concept evaluation, and method adoption across the two phases. This approach is also not exclusive to a single methodology developer and a single product sponsor. Instead, it can involve larger groups of developers and sponsors who may have ready applications for the developed tools within their current drug development pipelines. More information about this type of teaming approach can be found at Section 4.5.

2.3.2. Technical Areas (TAs) and Product Sponsors

CATALYST will create predictive modeling platforms for qualified drug safety applications by utilizing AI/ML modeling, supported by data capture in public and governmental spaces, and by developing novel

methods to address data gaps and validate the platforms. The development of underlying technologies will facilitate the generation of human-relevant data, enabling the production of verifiable and comparable datasets. The program components include three technical areas (TA): data discovery methods and predictive drug safety models (TA1), living systems tools for model development (TA2), and *in silico* simulation-based human physiology models (TA3).

TA1, Data discovery methods for predictive drug safety models
TA1 performers will capture and unify a wide range of existing preclinical, clinical, and electronic medical record (EMR) datasets that are available in the public and government domains, harmonize and curate these in a repository that can also integrate future datasets from the method development community, and produce a GXP environment and data governance platform to assure data quality and security. TA1 will procure foundation datasets for accurate deep learning methodologies to be developed within the team. The platform should also incorporate enhanced governance features for security, privacy and access control. The end result of this TA is the compilation of existing data into a framework that, either alone or with data gathered from TA2 and TA3, can be used to predict ADME-tox for a given drug.

TA2, Living systems tools for model development
TA2 will utilize both existing and emerging technologies, such as human and animal MPS, organoids, instrumented tissues, and *ex vivo* models to develop innovative tools that will generate datasets to inform the model development to occur in TA3. TA2 should be integrated with the other TAs that require data generation using novel methods for model development. TA2 technologies will result in novel data streams that understand, at fundamental levels, human physiology and its direct interaction with candidate pharmaceuticals.

TA3, *In silico* human physiology models
TA3 will utilize the datasets prepared and produced by TA1 and TA2 to generate and train *generalized* predictive platforms that are interpretable and explainable using various mathematical rules and AI algorithms and test the fidelity of the platforms using validated datasets (TA1 and TA2) and methods (TA2). Trained models should take multiple chemical, biochemical, and preclinical inputs and produce whole human predictive ADME-Tox modeling, including confidence metrics and other detailed outputs, needed for GXP validation and inclusion in IND submissions.

In addition to the identified TAs, the proposer[1] teams for CATALYST should identify a pharmaceutical product sponsor as an enabling element of the program and must have a Product Sponsor on their team within twelve months of award. The Product Sponsor will implement the methodologies created in CATALYST Phase I to IND-enabling studies that will be performed in Phase II. Although the bulk of their work will be in Phase II, their inclusion in the team during Phase I will allow for the evaluation of COU and other product specific requirements for the tools in creation.

Product Sponsor, Novel drug development activity
The Product Sponsor will test the predictive platforms for specific COUs and provide feedback to refine TA1/2/3 for regulatory qualifications. As a drug developer, the Product Sponsor will utilize the platforms developed in Phase I of CATALYST in IND-enabling applications and regulatory submissions in Phase II.

2.3.3. Proposal Options

[1] Proposer refers to all respondents to this Innovative Solutions Opening at all stages of the ISO.

Applicants may submit proposals for one of the following options:

Option A) A focused proposal targeting only TA1
Option B) A focused proposal targeting both TA2 and TA3
Option C) A comprehensive proposal addressing TA1, TA2, and TA3

The proposer teams for all options should include a Product Sponsor, as the proposer team's ability to execute Phase I and Phase II will be evaluated in evaluation Criterion #2 (see Section 6.1.2). Proposals addressing combination of TAs other than the specified options will **not** be reviewed.

2.3.3.1. TA1, Data discovery methods for predictive drug safety models

TA1 will build the tools needed to develop deep-learning approaches to predict drug safety from large data sets while also discovering, cataloging, and creating repositories for the community to use. This platform will be equipped with a range of tools that can curate and harmonize publicly available data and leverage non-public data also. With the anticipation of large datasets produced from CATALYST teams, TA1 will facilitate and implement data standardization and automated data curation in data generation workflow as well.

An *in silico* human physiology simulation platform that is capable of producing data to support IND application will need to incorporate pharmacokinetic/pharmacodynamic (PK/PD) models that have been developed and refined over decades, while also seamlessly integrating sophisticated human physiology models. A central data and model repository, underpinning the platform, should encompass all aspects of human biology, ranging from the molecular level understanding of xenobiotic properties and their interaction with proteome through macroscopic human physiological effects. Modeling a physiology-level simulation requires many diverse data types. There is a vast accumulation of data from clinical/preclinical studies and DMPK (Drug Metabolism and PK) studies, which are readily available in the public domain through databases such as PubChem, DrugBank, and ChEMBL. In addition to this, other relevant data such as physicochemical properties of compounds and biologics, anatomical and physiological data, molecular-level biochemical data, and pathophysiological data are necessary. These can be combined with specific disease or patient information. An inclusive structural database, either containing predicted or experimental data on protein-protein or protein-small molecule interactions, is another essential element. The ability to predict critical points in metabolic pathways where perturbation by small molecules or biologics have in systemic effect is also crucial. Additionally, being able to predict allergenicity, immunogenicity, or non-specific interactions can be important for biologics.

While data available in the bioinformatics databases are vast in both variety and depth, including genomic sequences, experimental or predicted protein structures, metabolic pathways, xenobiotic degradation and elimination, and allergenicity or immunogenicity of protein modalities, it is critical to acknowledge that these databases often contain inaccurate or missing annotations and are not yet formatted for ML applications. Therefore, addressing these issues are vital for AI/ML-centric data curation effort and would be required for the models developed by TA1 to be accurate in their predictive potential.

A successful proposal should consider each of the following, and provide strategies to achieve each goal:

- A plan to coordinate data across TA2 and TA3 (if being pursued by the proposer team) by providing a centralized data repository platform. This platform should be capable of communicating with and be compatible with the data enclave established by the program through the development and harmonization of data dictionaries.
    - Coordination and collaboration plan with the data enclave
    - Components of a data repository
    - Components of a data dictionary

- Data integration from diverse biomedical data types across biological principals. The database should include, but not limited to:
    - Physicochemical property data; description of molecular weight, solubility, absorption characteristics, distribution behaviors, and stability that are critical to assess bioavailability
    - Genomic and proteomic data; experimental and predicted protein structures, and expression and protein-protein interactions to understand pathways and therapeutic targets
    - Metabolic and signaling pathway data; enzymatic activities, reaction kinetics, and specific pathways involved in the metabolism and biotransformation to understand xenobiotic metabolism
    - Immunological data; allergenicity and immunogenicity of various haptens and protein modalities to predict immune responses to assess profiles
    - Physiological and pathophysiological data; anatomical, physiological, and pathophysiological data, including tissue-specific information and variations due to diseases or patient-specific factors for accurate modeling
- To achieve data integration, the proposal and developed platform should consider:
    - Automated data ingestion and preparation
        - Data quality enhancement
        - AI-guided data exploration and analysis
    - Pattern and anomaly detection
    - Data standardization
    - Data cleaning and normalization
    - Ontology integration
    - Quality assurance
    - Implementation of API for user accessibility
- Discussion of potential obstacles that could require a revision in the work plan or milestones with a discussion of alternative approaches.
- Detailed schedule or timeline for each milestone and the overall goal.
- Coordination with other TAs:
    - Close coordination with TA2 to integrate data from novel methods
    - Collaboration with TA3 to ensure data is AI/ML-ready and aligns with modeling platform requirements

By carefully curating publicly available bioinformatics databases, and potentially leveraging additional sources of data, TA1 teams will effectively integrate into a robust, high-quality repository that is ready for utilization in AI/ML applications. TA1 teams will then use these data to develop purpose built deep-learning models to be applied to CATALYST objectives. This repository and associated models can also serve as a crucial resource for developing *in silico* human physiology simulation platforms, ultimately contributing to advancements in the drug development process.

The TA1 metrics are outlined in **Table 2** of Section 2.4.2. Monthly technical and financial status reports will be required and discussed with the ARPA-H Program Manager Team at monthly meetings. ARPA-H may request performer data as deemed necessary throughout the program to verify the project progress. The datasets, toolkits, and the pipeline developed by performers will be shared with Independent Verification & Validation (IV&V), which may consist of extramural and intramural USG labs, for analysis and comparison. Additionally, they may also serve as IV&V during certain phases of the program to verify findings.

2.3.3.2. TA2, Living systems tools for model development

TA2 aims to develop and deploy innovative tools based on *in vitro* and *ex vivo* models to enhance data collection and analysis to *fill gaps present in the current data landscape*. These gaps include the lack of data based on human systems, the need for higher throughput generation of the quality of data needed to model human physiology, and better integration of living systems to reflect human complexity. To accomplish this, TA2 will leverage biological models such as MPS, organoids, instrumented tissues, and *ex vivo* models. In addition, comparator animal models can be developed to assess vast preclinical animal study data. Most importantly, TA2 will strategically select and develop novel models in close collaboration with TA3 at the start of the program, focusing specifically on systems and pathophysiological states that the project team is targeting. The targeted system should pose significant medical challenges due to its complex nature and disease implications, ensuring that these novel methods are valuable tools in advancing pharmaceutical research.

A successful proposal should consider each of the following, and provide strategies to achieve each goal:

- Identification of the current state of the art (SOA) and plans for improvement to achieve the objective of closing the data gap.
    - Close coordination with TA1 to scope the scientific and clinical data landscape, identify data gaps, and design and develop novel tools to bridge those gaps.
    - Close collaboration with TA3 to identify limitations of the current SOA prediction platforms and design and develop novel tools to improve predictability through the generation of relevant data.
- Innovation and integration of data collection
    - Integration of real-time sensor readouts
    - Integration of high-resolution, non-invasive and non-disruptive imaging
    - Implementation of multi-omics technologies in the analysis pipeline
    - AI/ML-ready data generation following the data dictionary set by TA1
- Consideration of biomarker identification for endpoint analysis
- Consideration of comparator models with animal cell lines
- Incorporation of genetic diversities into physiology models
- Platform standardization and guaranteed reproducibility
- Discussion of potential obstacles that could require a revision in the work plan or milestones with a discussion of alternative approaches.
- Detailed schedule or timeline for each milestone and the overall goal
- Coordination with other TAs:
    - Close coordination with TA1 to ensure data generated aligns with the data dictionary and is AI/ML-ready.
    - Collaboration with TA3 to strategically select and develop novel models that address limitations in current prediction platforms.

The TA2 metrics are outlined in **Table 3** of Section 2.4.3. Monthly technical and financial status reports will be required and discussed with the ARPA-H Program Manager Team. ARPA-H may request performer data as deemed necessary throughout the program to verify the project progress. The datasets, toolkits, and the pipeline developed by performers will be shared with IV&V, which may consist of extramural and intramural USG labs, for analysis and comparison. Additionally, they may also serve as IV&V during certain phases of the program to verify findings.

2.3.3.3. TA3, *In silico* human physiology models

TA3 aims to achieve *revolutionary* improvements in mechanistic models to address the limitations of current models and provide a more comprehensive and accurate representation of human physiology that

is capable of generating *animal-free* IND-enabling data through collaboration with TA1 and TA2.

Recent advancements in computational science and the surge of cheminformatics and multi-omics data have significantly influenced the field of drug discovery and development. Computational modeling is at the core of drug discovery in the post-genomic era, aiding in various processes such as chemical space sampling, lead scaffold identification, implementation of synthesizability in chemical design, and risk mitigation in lead compound selection. The field of biologics development has also benefited from computational approaches, particularly in improving functional capabilities, *de novo* protein design, enhancing manufacturability and extending half-life.

The failure of clinical trials represents a missed opportunity to offer treatment options to patients. Historically, high rate of clinical trial failures and post-market drug attrition rates have been attributed to toxicity and lack of efficacy. This is in part due to inadequate predictive capabilities of preclinical tools such as animal studies and *in vitro* models. While ongoing efforts aim to enhance human relevance in preclinical studies, the risk of clinical trial failures can be greatly reduced if accurate PK/PD modeling is possible with human relevant data, and drug attrition can be mitigated if clinical trials can predict chronic and idiosyncratic toxicities by accounting all population diversity into clinical trial subjects.

Pharmacometrics aims to mathematically model and simulate the ADME processes in both drug development and clinical application. There are two major types of models utilized: data-driven empirical models and hypothesis-driven mechanistic models. Empirical models, such as population PK, describe observed data and may include physiological parameters to account for individual variability in pharmacokinetics. On the other hand, mechanistic models provide a mathematical explanation of the drug ADME processes by leveraging physiological parameters and *in vitro* data.

Mechanistic models, particularly physiologically-based pharmacokinetic (PBPK) models, have been increasingly successful in achieving regulatory waiver from the FDA and EMA for drug applications, effectively addressing questions such as absorption modeling and manufacturing quality support in scale-up and post-approval changes (SUPAC). However, revolutionary advances need to be made for mechanistic PK/PD predictive simulators by incorporating more human-relevant data, intensive sampling of cellular-level information, and a comprehensive understanding of human metabolism and cell signaling at the biochemical and molecular levels.

A successful proposal should consider each of the following, and provide strategies to achieve each goal:

- Identification of the current state of the art (SOA) and plans for improvement in predictability of simulation platforms.
    - Leverage recent advancements in the computational science of AI/ML
    - Integration of proteome-wide understanding of xenobiotic metabolism
    - Promotion of technical push in TA2 through identification of data requirements for model development
    - Safety and toxicity prediction
    - Verification of platforms through close collaboration with TA1 and TA2
- Healthy physiology modeling with safety and toxicology focus.
    - Broad impact of safety and toxicology in drug discovery and development
    - Prediction of biological pathways and biomarkers and endpoints for acute and chronic toxicity
    - Inclusion of genetic, environmental, and dietary factors for individual-specific modeling
    - Equity and health impact consideration
- Future-proof expandability and flexibility for application in other disease area.
    - Consideration of platform design to allow integration of new data and models

    - Close collaboration with TA1 and TA2 to standardize the input data format
    - Expandable for complex simulations
- Discussion of potential obstacles that could require a revision in the work plan or milestones with a discussion of alternative approaches.
- Detailed schedule or timeline for each milestone and the overall goal.
- Coordination with other TAs:
    - Close collaboration with TA1 to utilize curated data repository and ensure data is in standardized format
    - Coordination with TA2 to identify data requirements and integrate data from novel methods
    - Work with TA1 and TA2 to verify and validate developed platforms

The TA3 metrics outlined in **Table 4** of Section 2.4.4 will increase in difficulty and complexity over the course of the CATALYST program. Monthly technical and financial status reports will be required and discussed with the ARPA-H Program Manager Team. ARPA-H may request performer data as deemed necessary throughout the program to verify the project progress. The datasets, toolkits, and the pipeline developed by performers will be shared with IV&V, which may consist of extramural and intramural USG labs, for analysis and comparison. Additionally, they may also serve as IV&V during certain phases of the program to verify findings.

2.3.3.4. Product Sponsor, Novel drug development activity

In silico simulation platforms bring myriad benefits, including reduced development costs, decreased drug development timelines, and enhanced predictive capacities for drug safety and efficacy profiles. The platforms developed by TA1/2/3 performers must achieve these potentials for real-world applications.

During the Phase I of CATALYST, Product Sponsor(s) will play an advisory role for performer teams in various aspects of the project. They will provide guidance on disease area selection, ensuring that the chosen areas align with the program's objectives and have the potential for significant impact. Additionally, Product Sponsor(s) will offer their expertise in navigating the drug development tool qualification process, working closely with the teams to ensure that the *in silico* platforms meet the required standards and are suitable for use in IND application. They will also contribute to FDA IND-application process, assisting in the preparation and submission of necessary documents and communicating with the regulatory agency. As a liaison between the FDA and the performer teams, Product Sponsor(s) will facilitate effective communication and collaboration, helping to streamline the development and validation of the *in silico* platforms.

In Phase II, Product Sponsor will test these innovative tools in real-world scenarios by implementing these platforms in their drug development process. They will validate and verify the platforms by comparing the results with their own preclinical and clinical study results. Ultimately, Product Sponsor will evaluate whether the simulation data produced through the platforms has the predictive power to replace the current practice of preclinical IND-enabling studies. The evaluation will also include the identification of potential improvement areas of the platforms. With this objective in mind, Product Sponsor should be in the late stage of the drug discovery process or the early development stage, having identified and validated potential drug targets and lead molecules, to participate in the program.

A successful proposal should include the following for Product Sponsor in Phase I, and provide strategies to achieve each goal:

- Past experience and success in drug development tool (DDT) development
- Disease area target selection and fit-for-use identification together with TA1/2/3

- Intellectual property (IP), market analysis and commercialization strategies
- Stakeholder identification and engagement
- Regulatory approval strategy

In addition, the proposal should include the following for Phase II, and provide strategies to achieve each goal:

- Possession of validated drug targets and lead molecules.
    - Produce pseudo-clinical data by leveraging the technologies developed by TA1/2/3
    - The lead molecule should be validated through medicinal chemistry studies (structure-activity relationship, or SAR), as well as in vitro and in vivo studies focusing on the mechanism of action (MOA) or mode of inhibition (MOI). Additionally, rescreening should be performed
    - Available preclinical data, which can be compared to and validative of the IND-enabling novel *in vitro/ex vivo* models and simulation platforms developed in TA1/2/3
    - Identified therapeutic indications, correlated biomarkers, and efficacy endpoints for the validated drug targets and lead molecules
- Pre-IND and IND-application plans.
    - Plan for *in silico* simulation platform integration and evaluation
    - FIH clinical trial design and pre-IND meeting
    - Sharing of clinical study data with the TA1/2/3 team
- Consideration of disease area to promote equity of the program.
- Consideration of collaboration and data sharing strategy with TA1/2/3 performers.
- Discussion of potential obstacles that could require a revision in the work plan or milestones with a discussion of alternative approaches.
- Detailed schedule or timeline for each milestone and the overall goal.

The Product Sponsor's requirements and metrics are outlined in **Table 5** of Section 2.4.5. Monthly technical and financial status reports will be required and discussed with the ARPA-H Program Manager Team. ARPA-H may request performer data as deemed necessary throughout the program to verify the project progress. The datasets, toolkits, and the pipeline developed by performers will be shared with IV&V, which may consist of extramural and intramural USG labs, for analysis and comparison. Additionally, they may also serve as IV&V during certain phases of the program to verify findings.

2.3.4. Program Execution and Options

Timeline: The overall CATALYST timeline is structured as a 54-month effort consisting of 2 phases; Phase I with a 36-month effort and Phase II with an 18-month effort. Phase I will integrate pre-clinical and clinical publicly available study data available, as well as discover methods to use non-publicly available data, to develop predictive deep-learning models (TA1) while also generating exploratory and validation data using novel living systems methods (TA2) for multi-system *in silico* physiology model development and validation (TA3). Phase II will be spearheaded by Product Sponsor(s), who will carry out the IND application while contracting the methodologies developed in CATALYST Phase I without experimentation.

Structure: In Phase I, TA1/2/3 performers will focus on developing predictive *in silico* platforms, and the submitted proposals should address all TAs, TA1 only, or TA2 and TA3 only (see Section 2.3.2). The ML-centric comparative data generation for modeling will take place within TA2, while TA1 will curate the data from TA2 as well as the existing relevant data in the public and USG space. Additionally, the curated data will be accessed and discovered through novel means. Predictive platform design will occur in TA3

using the training data curated by TA1.

Down-Selection: The baseline performance testing for validation and verification of the platform will be done at the end of Month 18, with the datasets set aside for this specific purpose by TA1. The performers will be asked to provide assessment metrics for the stage. In consultation with ARPA-H program management and commercialization/regulatory experts, the performer team will identify the COU of the predictive model by making minimal modifications to the platform algorithms to ensure its suitability for specific purposes. Additional data generation through new experimentations by TA2 and iteration will be necessary to improve models. The iteration steps should be done through collaboration among all TA performers and Product Sponsor.

The performance validation and verification of the platform by IV&V will be carried out at the end of 30-month using datasets and government partner validation capabilities that are unique to the CATALYST program. The performers will spend the final 6 months in platform refinement. The performer teams that successfully complete the verification stages will have the opportunity to bring their predictive platform to regulatory COU qualification process or another FDA-qualification program (such as the Innovative Science and Technology Approaches for New Drugs (ISTAND) Pilot Program, which will assess the platform's ability to meet the necessary standards for regulatory purposes. The platforms should also satisfy other FDA guidance (e.g., FDA-2013-D-1464, FDA-2019-D-2398, FDA-2020-D-1517, etc.) for pharmacometric modeling. This will ensure that the platforms are compliant with the current FDA guidance. All performers should also develop an FDA engagement plan prior to CATALYST inauguration to understand and familiarize themselves with the FDA's guidelines and requirements for predictive platforms.

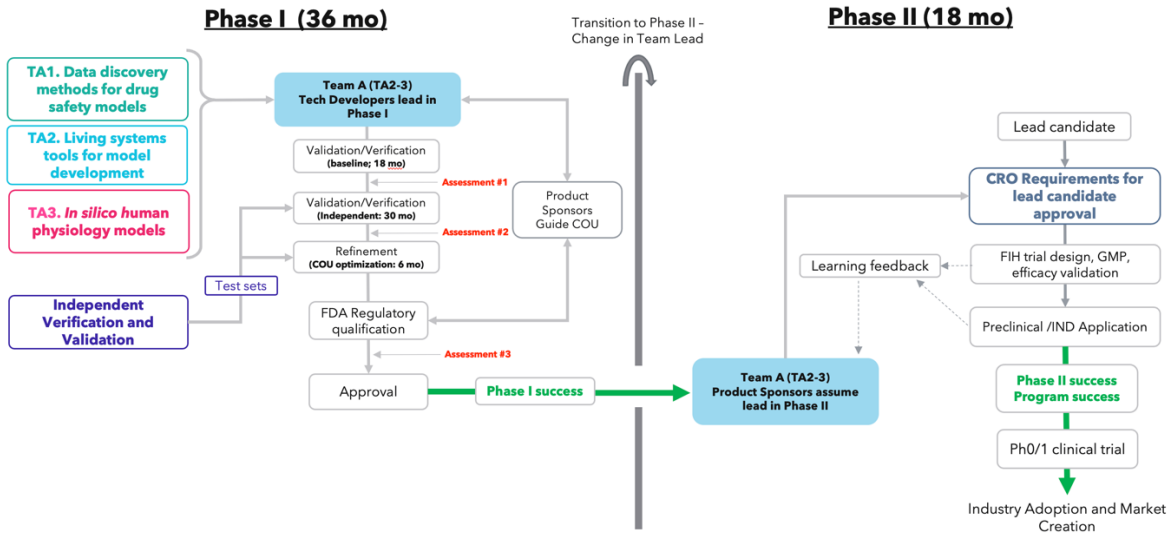

Figure 3. The program structure and timeline of CATALYST by phase and TAs. TA: technical area, mo: month, SOA: state of the art, COU: context of use, IND: investigational new drug (application), FIH: first in human.

Performers who have successfully developed a predictive prototype platform, which incorporates comprehensive coverage of human physiology and ADME-Tox information for drug profile prediction and have accomplished Phase I milestones and IV&V verification/validation, will be considered for CATALYST Phase II, which will be led by Product Sponsor within the proposer team. During Phase II, the performers will concentrate on concurrently developing pharmaceutical candidates through both traditional

animal testing, *in vitro* models and pilot digital pathways. The transition phase is designed to facilitate the integration of predictive platforms and data across multiple performers, and to select the optimal sources for preclinical and clinical study candidates. Phase II involves the creation of product regulatory filings using digital-only data or hybrid of digital data and *in vitro* model data (*No Animal Challenge*) for the FDA.

Proposal Requirements: To ensure the applicability of tools developed to the broader community and for the success of CATALYST platforms, performers must have demonstrated team capabilities per the selection of TA submission pathway. Proposals that fail to address the technical area(s) required, as noted above, will be deemed non-conforming and may be rejected without further review. The proposal must also include data and platform access plans and commercialization plans including FDA meeting milestones, technology transfer milestones, platform proof-of-concept objectives, and market analysis and partnership models for commercialization. The predictive platforms must meet the specifications listed in Section 2.4.

2.3.5. ELSI

ARPA-H is committed to developing an *in silico* platform for drug development that will test PK/PD while carefully considering the ethical, legal, and social implications (ELSI) for broad subpopulations of Americans. The platform can address the challenges faced by drug developers when considering diverse subpopulations, such as individuals with various genetic, metabolic, age, and health characteristics, into clinical trials. By considering the broad spectrum of human diversity, the platform aims to promote more inclusive and equitable drug development processes.

ELSI objectives for the *in silico* platform may include:

- Ensuring equitable representation of diverse subpopulations in the platform's data and models.
- Addressing disparities in drug efficacy and safety across different subpopulations.
- Minimizing risks to vulnerable populations, such as pregnant women, fetuses, and children.
- Enhancing pediatric drug development by prioritizing safe and effective dosing regimens.
- Protecting patient privacy and data security in compliance with relevant laws and regulations.
- Fostering transparency and public trust through open communication with stakeholders.

The *in silico* platform should be designed to address the challenges associated with clinical trial design and account for population diversity by: 1) simulating diverse subpopulations to predict drug responses in groups that may be difficult to include in clinical studies, 2) predicting complex drug-drug interactions and optimizing dosing regimens for various subpopulations, and 3) informing and optimizing clinical trial design to ensure trials are more representative of diverse patient populations.

By prioritizing these ELSI objectives, ARPA-H can contribute to the development of safer, more effective, and more equitable therapeutics for all Americans.

2.3.6. Data Management and Sharing Plan (DMSP)

The DMSP shall include all information included in the Six Element plan format recommended by the National Institutes of Health (to view the Six Element suggested format visit https://grants.nih.gov/grants/forms/data-management-and-sharing-plan-format-page). The six elements are:

1. Data Type
2. Related Tools, Software and/or Code
3. Standards
4. Data Preservation, Access, and Associated Timelines

5. Access, Distribution, or Reuse Considerations
6. Oversight of Data Management and Sharing

Within the DMSP, proposers for each TA must include a detailed plan of what types of data, platforms, or portions of platforms they will be sharing with the scientific community as a result of the program. All non-proprietary data should be shared with the scientific community promptly within a year of generation. The specific repository method should be discussed and chosen in agreement with the ARPA-H program manager. In addition, the proposers must provide an explicit plan for timely material, data, and platform exchange between all team members on the proposal, as the free flow of information is critical for the success of the predictive platform development and its verification. The data should be transmitted frequently, in a timely manner, and in its entirety. The development of living systems tools by TA2 and their dissemination will require performers to prepare plans for sharing and distribution of non-data resources that will be generated by the proposed project, including cell line origin, experimental tools and specifications, protocols, biomaterials, and reagents.

The proposers will need to present explicit solutions to address the significant data storage and computing challenges presented by the program, with the understanding that the plans and repository may change later in the program.

2.3.7. Assessment Checkpoints

The program metrics state the assessment decisions in Section 2.4 and the down selection description in Section 2.3.3. When specific end-of-phase metrics are not met, a No-Go decision is made. To transition to Phase II, performers must have a Product Sponsor partner as an element of the CATALYST agreement. The Product Sponsor will utilize their predictive *in silico* platforms for IND applications, and the platform must be acceptable for regulatory purposes by the FDA. Any performer that is non-compliant to the data sharing requirements or the equity requirements may not be selected for Phase II.

2.4. Program Goals and Metrics

To evaluate the effectiveness of a proposed solution in achieving the stated program objectives, the following program goals and metrics will serve as the basis for determination of satisfactory progress to warrant continued funding. Although the program metrics are specified below, proposers should note that the Government has identified these goals with the intention of bounding the scope of effort while affording maximum flexibility, creativity, and innovation of proposed solutions to the goals. Proposals must cite the quantitative and qualitative success criteria that the effort will achieve at each phase's program milestone, as well as the measurement of intermediary metrics. If the metrics are not meaningful for a particular case, proposers are expected to provide their own metrics and describe the quantitative improvement that those metrics represent over the state-of-the-art. Power analysis calculations may be needed to support the proposed metrics.

2.4.1. Overall Program Goals

The overall objectives of CATALYST are listed in **Table 1** and should be referenced within the context of individual project efforts. Progress checks for Phase I include the creation of team roadmaps for constructing the *in silico* ADME-Tox and biodistribution/tox platform, supported by preliminary results generated by the teams. Interim assessments include the down-selection of the most promising platform approaches verified by the IV&V, and the use of the platforms by product development teams. The end of Phase II assessments for CATALYST focuses on the ability to fully replace animal models by the parallel development of animal-free *in silico* and *in vitro/ex vivo* approaches in IND-enabling data production. This

results in final assessments where novel drug developers file IND applications based on data from only animal-free *in silico* studies.

Table 1. Overall CATALYST Objectives

Objective	Specifics
Data repository	• Establish a data repository for current platform improvement and a foundation for future development • Capture relevant data, such as cheminformatics, toxicological, metabolic, and multi-omics data • Facilitate data sharing among different stakeholders
Living systems tool	• Develop innovative tools to mimic living systems for the purpose of testing drug safety and toxicity • Integrate high throughput capability, efficient sensing of perturbation, and reproducibility • Utilize human-relevant models and comparator animal models to improve reliability and predictive power
Purpose-built AI/ML *in silico* platform	• Develop simulation platforms for animal-free IND-enabling data generation • Create platform APIs that are user-friendly, scalable, and accessible to the scientific community
Demonstration of platform capabilities	• Conduct a pilot hybrid drug development project using both *in silico* and in vitro/ex vivo models to demonstrate the capabilities of the *in silico* platform • Showcase the platforms through IND-enabling data generation without relying on animal studies in select disease targets • Obtain COU regulatory approval of the platform • Design FIH clinical trials using the animal-free *in silico* platform
Platform transition and commercialization	• By 18 months, develop a comprehensive plan for transitioning *in silico* platforms for commercial drug development use • Identify industry partners for platform maturation • Resolve additional technical, IP and regulatory challenges • Expand the capabilities to other disease models

The expected metrics and assessment decision points are listed in **Table 4** for performers with TA3. In addition to frequent performance reviews throughout the phases, performers must provide an end-of-phase final report that summarizes all efforts and data for each completed CATALYST Phase.

Note that in their proposals, performers must provide relevant quantitative and qualitative metrics by task besides the assessment decision points set by this announcement in **Table 4**. Performers who have not had experience in DDTs development must seek consultations with project management experts with experiences in setting milestones and metrics, as well as in crafting GANTT charts, overlaying timelines of critical activities, and platform development plans.

2.4.2. TA1 Metrics

The expected TA1 metrics for Phase I are listed in **Table 2**.

Table 2. TA1 Metrics of CATALYST Phase I

Metrics	Specifications
Repository	Scalable preclinical and clinical data repository that accepts biological and chemical

platform requirements for data curation and harmonization to achieve data discovery	data • Identification and utilization of existing preclinical and clinical study data (Percent usability ≥ 90%) • Percentage of data fields normalized and harmonized across sources (95%) • Establish data model for the data generated by the program performers and CATALYST-adjacent ARPA-H projects (Precent data type coverage = 100%) • Automated data annotation and curation to a repository for AI/ML training (Target efficiency ≥ 70% , Curation accuracy ≥ 95%) • Data repository completeness and accuracy (Target = 100%) • Data imputation on missing or corrupt data (Success rate ≥ 95%, Accuracy to ground truth ≥ 90%) • Security metrics embedded in the platform. 256-bit encryption applied to 100% of data at rest and in transit. Provide monthly security scans and penetration test + Practice FAIR (Findable, Accessible, Interoperable, Reusable) Principles in managing data • The repository should have additional quality dimensions captured
Data standardization requirements for repository platform	Proper curation and storage of data in machine-readable form in public and project-generated databases in formats such as CSV, JSON, XML, and FASTA • Establishing metadata standards, and standards for integrating data from diverse sources and formats, including data normalization, and transformation (Completeness of metadata annotation standardization ≥ 95%) • Unification of data format and dimensions to increase usability for AI/ML training o Proper annotation, creating sets of ontologies (at least 20 for each data type), and minimum information standards o Frequency of missing values should not exceed 5% any data field and 1% overall o Frequency of outliers (using Z-score / interquartile range) should not exceed 2% for any data field • Coordination with performer teams to compile database that is secure, accountable, and accessible to a broad scientific community
Relevant feeder databases	Cheminformatics, genomics, proteomics, signaling and metabolic pathways, protein structure, drug binding, protein-small molecule interaction, protein-protein interaction, enzyme reaction and annotation, toxicological data, systems biology data including physiological data, preclinical study, clinical study, clinical data (EHR)
Data enclave	Data curation and harmonization utilizing the platform • Construction of data enclave (i.e. access control, data governance, data infrastructure, and data sharing). • Datasets to effectively train and validate simulation models developed by TA3. These data can include (but not limited to) experimental assay data, structural biology data, multi-omics data, and PKPD data including ADME-T-related protein functions.
Predictive Model Parameters	Predictive models that leverage state-of-the-art AI/ML models, especially deep learning, include generative and discriminative models using artificial neural networks.

	• Training dataset: incorporation into database curated in TA1. Ensure the ability to scale the training dataset by at least 10X to accommodate future growth and model complexity • Validation & Testing dataset: Evaluation of performance of the model platforms. Utilize a robust strategy (e.g., cross-validation, holdout validation) with clearly defined: o Validation set: hyperparameter tuning and model selection. (For classification task, aim for a class distribution where ratio of the majority class to the minority class is within a specified range (e.g., no more than 4:1) o Test set: final unbiased performance evaluation. Model performance: • Baseline comparison: Use a native model or rule-based approach. SOA models should be benchmarked against 1-2 existing SOA methods. • Classification: Utilization of performance metrics such as Accuracy, Precision, Recall, F1 score and Area under the receiver operating characteristic curve (AUROC), etc. • Regression: Mean Squared Error (MSE), Mean Absolute Error (MAE) and Root Mean Square Error (RMSE); test up to 3 additional independent datasets for validation • Consider task-specific metrics for other SOA models
Data and Platform sharing	1. Sharing of data and platforms produced during the program cycle with ARPA-H and TA teams. 2. Sharing IP-worthy proprietary result with TA teams; consult with ARPA-H Program Manager Team

2.4.3. TA2 Metrics

The expected TA2 metrics for Phase I are listed in **Table 3**.

Table 3. TA2 Metrics of CATALYST Phase I

Metrics	Specifications
Organ- or physiological system-level tools	Combining multiple CIVMs (eg., organoids, organ-on-chip, instrumented tissues) or *ex vivo* models (eg., bio-printed tissue, precision-cut tissue slices) to generate comprehensive *in vitro* models that accurately replicate system-level responses when exposed to xenobiotics or biologics, enabling precise evaluation of healthy state representation • Correlation coefficient (r) between in vitro/ex vivo models and human in vivo response ($r \geq 0.9$) • Mixing multiple model systems for complex representation (Target, ≥ 3) • Accuracy of *in silico* modeling in predicting organ-level response ($\geq 80\%$) • Represent human physiology of tissue, organ or system (Target, ≥ 3) • The endpoint analysis showing correct biomarkers relevant for safety and toxicity (Accuracy target, $\geq 90\%$) • Implementation of high throughput capabilities (Number of samples =100, Automation level $\geq 80\%$) • Further development to represent genetic diversity through primary cell lines, or genetically manipulated cells, using technology such as CRISPR-Cas9 or other methods to leverage cell origins representing age, gender, genetic and metabolic background reflecting diverse American population

	• Statistical power analysis to ensure adequate sample sizes are met.
Equity consideration for challenging clinical trial groups	Physiology model through combination of system-level models to simulate safety and toxicity. Examples of such models can be: • Reproductive women's health or fetal drug effects • Difference of drug responses to genetic and environmental backgrounds • Drug effects on pediatric, geriatric or metabolically challenging population
Animal comparator in vitro models	1. Twin to human organ- or physiology-level models that can produce comparable data 2. The system should serve the purpose of model verification when used in conjunction with a test dataset
Endpoint analysis and biomarker development	Utilization of existing and de novo analysis tools that have the following capabilities: • Integrated sensor system with online, on-demand, real-time capabilities to measure genomic, epigenetic, transcriptomic, proteomic, and metabolic analyses, and combination of multiple of them o Number of parallel integration (Target, ≥ 2) o Measurement window (Target, ≤ days) • Compatibility with off-line measurement through downstream process for multi-omics technology (Compatibility ≥ 2 separate measurements) • Real-time visualization of cell and tissue level activities o Spatio-temporal resolution (Subcellular level with ≤10 sec minimal measurement interval) o Visualization channel (Target, ≥ 3) • Seamless data integration into TA1 platform
Platform Standardization	1. Standardization of technologies such as cell lines, device form factor, and readouts that can be adopted by the wider basic, translational, and regulatory science community 2. Reportability, reliability metrics, cell line optimization and standardization that are fit-for-use preclinical data generation for IND application
Data sharing	1. Deposition of the data produced during the program cycle to the program data repository for evaluation by ARPA-H and TA teams. 2. Sharing IP-worthy proprietary result with TA teams; consult with ARPA-H Program Manager Team

2.4.4. TA3 Metrics

The expected TA3 metrics and Assessment decision points in Phase I are listed in **Table 4**.

Table 4. TA3 Metrics of CATALYST Phase I

Metrics	Specifications
Modeling and simulation platform baseline requirement	1. Improvement to the existing *in silico* models such as PBPK (including PBAM and PBBM) ADME-T, PK/PD, DDI, QSP/QST and E-R for regulatory applications 2. Proteome-scale understanding of target interaction and metabolism of biologics and xenobiotics, including the parent compounds and their metabolites 3. Verification metrics: each predictor should include performance metrics that are defined in this table or by the performers and can be independently verified and validated 4. For classification and egression models, follow the detailed specifications in TA1 for further guidance on the models' metrics. For deep learning models, use

	applicable classification and regression metrics, and include additional metrics depending on the neutral network model used
Pharmacology and safety simulation	Prediction of physicochemical properties of compounds providing at minimum: MW, LogP, LogD, pKa, Kd to HSA, B:P ratio, site of modification (SOM)
	1. Prediction of ADME properties including but not limited to: • Induction of comprehensive list of Phase I and II enzymes, transporters, key metabolic enzymes • Prediction of Phase I and II metabolism, site of modification, and DDI • Prediction of interaction with drug transporters • Distribution of drugs accounting the following: age, pregnancy, diet. 2. Prediction of pharmacokinetics parameters including but not limited to: • Cmax, Tmax, area under the curve (AUC), Vd, $t_{1/2}$, Clearance (Cl). Up to 2-fold or less in prediction error depending on the parameters 3. Predicted parameters will be evaluated against test sets to obtain performance metrics such as accuracy, AUC, MAE, RMSE, and coefficient of determination (R^2) 4. The acceptable uncertainty for PK parameters (Tox) can be from 1.5 to 2-fold in prediction error.
Toxicology simulation	1. Toxicophore prediction using existing and new datasets: • Genotoxicity, mutagenicity, and chromosomal damage • Off-target activity to receptors, enzymes and channels • Immunotoxicity and photosafety • Reproductive and fetal toxicity • Development of additional toxicology endpoints beyond the current norms 2. Predicted parameters will be evaluated against test sets to obtain performance metrics such as accuracy, AUC, MAE, RMSE, and R^2
Validation and verification metrics	**1. Initial validation and verification at 18-mo for baseline testing** • IV&V will provide enclaved test sets for baseline performance testing • The calculation will be done using pure PK/PD modeling, without hybrid or empirical modeling • Satisfies FDA guidelines for computational modeling **2. Final independent validation and verification at 30-mo for assessment to proceed to regulatory qualifications** • IV&V will conduct the platform verification using enclaved test sets • The calculation will be done using pure PK/PD/GXP modeling, without hybrid or empirical modeling • PK/PD/GXP performance exceeds the 18-mo baseline performance by a minimum of **75%** across all verification metrics. • Satisfies FDA guidelines for computational modeling **3. Regulatory qualification at 36-mo to proceed to phase II** • Platform optimization for a minimum of 5 use cases and approval of the computational simulation platform by FDA for specific COU areas
Pre-IND parameter and clinical trial design and simulation	1. The model system is capable of simulating FIH clinical trial design parameters, such as: • Dose range identification; Dose escalation; Delivery procedure, route and duration; Drug formulation and manufacturing for Phase I trial; manufacturability and thermostability (biologics)

	2. On-boarding of Product Sponsors by 12-mo if not joined at the inception to lead pre-IND and IND tasks.
GXP simulation with formulation and manufacturing focus	FIH drug formulation development and performance optimization, and clinical trial and commercial formulation • Absorption and bioavailability; Patient physiology; Safety, manufacturability, and manufacturing parameters including excipient selection
Platform access	1. Access of the simulation platform produced during the program cycle for evaluation by ARPA-H and TA teams 2. Sharing IP-worthy proprietary result with TA teams; consult with ARPA-H Program Manager Team

Physiology-based absorption modeling (PBAM), Physiologically-based biopharmaceutics modeling (PBBM) Quantitative systems pharmacology (QSP), Quantitative systems toxicology (QST), Exposure-response (E-R)

2.4.5. Requirements for Proposer Team's Candidate Drug Product

The expected requirements for novel drug development activity are listed in **Table 5**.

Table 5. The requirements for novel drug development activity in CATALYST Phase I and II.

Requirement	Specifications
Possession of validated target and leads (Qualification)	Possession of validated drug target and lead molecules that can be applied for IND-enabling data generation utilizing the technologies develop in CATALYST Phase I. • Candidates that have not yet progressed to IND-enabling study data generation yet will be given priority – methodologies from Phase I are meant to replace existing tools, not to be performed in parallel • The new molecular entity is validated in medicinal chemistry (SAR), in vitro and in vivo studies (MOA/MOI and rescreening) • Preclinical data that can be compared to and recapitulated in complex in vitro models and simulation platform • Therapeutic indications, correlated biomarkers and efficacy endpoints • Disease area include metabolic, cancer, immune, musculoskeletal, neuromuscular among others
Clinical trial candidate (Qualification)	1. Special population consideration: hard to test with current clinical trial models due to technical, ethical and legal hurdle is also accepted • Pregnant women with fetal DDI • Diverse genetic and metabolic background • Pediatric dosing of drugs is essentially "off-label use"; not clinical efficacy, toxicity, dosing regimen studies • Pregnant women/lactating women/women of childbearing age • Elderly population • Other typically underrepresented populations in clinical trials • Completed clinical trial design, and the associated information needed, to submit an IND package with other preclinical/nonclinical data • Completed plan for FIH clinical trial execution after IND approval 2. Clinical trial design can account population diversity • Diverse genetic, epigenetic, dietary, lifestyle, age and gender factors that can't be included in the current clinical studies • Complex drug-drug interactions (polypharmacy) and dosing regimens that are difficult to predict

	3. Technology-driven implementation to maximize diversity, equity, and inclusion (DEI) in drug development and clinical trials 4. The simulation to provide safety and efficacy data that can replace human clinical trials
Platform evaluation	1. Guidance to platform refinement and evaluation 2. Assistance to the platform developer and provide qualification strategy
Proof-of-concept animal-free IND	1. Simulation informed formulation and GMP manufacturing for phase I clinical trial and optionally for exploratory trial 2. FIH clinical trial design and pre-IND meeting 3. Exploratory Phase 0 trial (optional) and Phase I clinical trial • Clear target product profile (TPP) including equity attribute • GMP manufacturing capability • Clinical trial site, study size, target population, study monitoring • Pharmacokinetics and efficacy biomarker endpoint analyses • Safety, ethics, and equity plan • FIH clinical trial-informed model improvement in all areas, and preparation of Phase II/III clinical trials
Clinical data sharing	1. Deposition of the data produced during the program cycle to the program data repository for evaluation by ARPA-H and TA teams. 2. Sharing IP-worthy proprietary result with TA teams; consult with ARPA-H Program Manager Team

2.5. General Requirements

2.5.1. Proposing Teams

If the teams do not start with a Product Sponsor identified, the performers can initiate performance. However, onboarding Product Sponsors to the team within the first 12 months of Phase I will be a requirement for TA2/3 and TA1/2/3 (see Section 2.3.2). Teams that do not have at least one Product Sponsor by the end of month 12 will be eliminated from the programs and their agreements will end. Additionally, the teaming structure created by the performers needs to be flexible enough to allow for the lead role to shift amongst members as needed as the program progresses through the phases and based on the project's requirements. The contracting mechanism will be Other Transaction (OT) only. No other type of contracting vehicle will be accepted or negotiated.

It is expected that proposals will involve teams with the expertise needed to achieve the goals of all proposed TAs. Specific content, communications, networking, and team formation are the sole responsibility of the proposer. A group or co-investigator may participate in multiple proposals. It is likely that performer teams will be collaborations between multiple for-profit companies with additional academic institution or NGO collaboration. We encourage performers to leverage regulatory expertise of product developers.

A full-time experienced Project Manager (PM) must be budgeted for in the proposal and must be hired by performers upon successful award to ensure efficient communication between performer teams, and with ARPA-H. A PM qualification description, whether named or if a PM is to be hired later, must be included as part of the proposal.

ARPA-H will hold a Proposers' Day (see Section 8, Other Information) to facilitate the formation of proposer teams and enable sharing of information among interested proposers. CATALYST's Teaming Profiles (https://arpa-h.gov/research-and-funding/programs/CATALYST/teaming) will be an additional platform for proposers to find co-performers, especially across all TAs, who may rarely work or are

unfamiliar with each other.

2.5.2. Diversity in clinical trial populations for CATALYST Phase II

While following the guidelines outlined by FDA on clinical trials, ARPA-H is also committed to equitable healthcare access irrespective of race, ethnicity, gender/gender identity, sexual orientation, disability, geography, employment, insurance, and socioeconomic status. CATALYST will ensure that all performers follow the FDA's guidance titled "Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials".

3. Award Strategy

The ISO constitutes a merit-based solicitation and uses merit-based competitive procedures to the maximum extent practicable. Multiple awards are anticipated under this ISO, but the number of awards made will depend on the quality of the proposals received, agency mission priorities, and the availability of funds. Proposals are expected to use innovative approaches that include novel technology, enabling revolutionary advances in medicine and healthcare.

The Government reserves the right to select for negotiation all, some, one, or none of the proposals received in response to this ISO and to make awards without negotiations with proposers. In the event that the Government desires to award only portions of a proposal, negotiations will commence upon selection notification. The Government also reserves the right to conduct negotiations if it is later determined to be necessary. Additionally, ARPA-H reserves the right to accept proposals in their entirety or to select only portions of proposals for negotiation and award. The Government reserves the right to fund proposals in phases, including as optional phases, as applicable. ARPA-H reserves the right to make multiple awards, a single award, or no awards. Multiple awards are anticipated.

Proposals identified for award negotiation will result in OTs. OTs are commercial-like contractual arrangements. Specific terms and conditions will be negotiated for each OT. An OT terms and conditions template will be provided if selected for award negotiations.

The Agreements Officer has sole discretion to negotiate all terms and conditions with selectees. ARPA-H will incorporate pre-publication reviews or other restrictions, as necessary, if it determines the research resulting from the proposed effort will present a high likelihood of disclosing sensitive information including Personally Identifiable Information (PII), Protected Health Information (PHI), financial records, proprietary data, and any information marked Sensitive but Unclassified (SBU), Controlled Unclassified Information (CUI), etc. Any award resulting from such a determination will include a requirement for ARPA-H permission before publishing any information or results on the program.

3.1. Solicitation Procedures

This ISO will be solicited through ARPA-H ISO external facing (public) website and SAM.gov. See Section 4 for solution summary and proposal preparation and submission information.

3.2. Award Information

The Government reserves the right to request any additional, necessary documentation to support the negotiation and award process. The Government reserves the right to remove a proposal from award consideration should the parties fail to reach agreement on award terms and conditions, cost, and/or if the proposer fails to provide requested additional information in a timely manner.

The ISO includes a bundle of attachments that contains proposal submission templates and a Model Agreement (Other Transaction) with basic terms and conditions. The bundles will be provided to proposers invited to submit a proposal. Proposers may submit red-line edits to the basic terms and conditions of the resulting instrument; however, the Government AO shall have the sole discretion to negotiate any red-line edits. Proposers not encouraged to submit a proposal may request the bundle in writing to CATALYST@arpa-h.gov after receiving notice of the ARPA-H's decision to discourage submission of a full proposal.

4. Eligibility Information

4.1. Eligible Applicants

All responsible sources capable of satisfying the Government's needs may submit a solution summary and/or proposal to this ISO. Specifically, universities, non-profit organizations, small businesses and other than small businesses, hospitals, community health centers and non-Federal research centers are eligible and encouraged to propose to this ISO as part of a CATALYST team.

4.2. Prohibition of Performer Participation from Federally Funded Research and Development Centers (FFRDCs) and other Government Entities

ARPA-H is primarily interested in responses to this solicitation from commercial performers, academia, non-profit organizations, etc. In certain circumstances, FFRDCs and government entities will have unique capabilities that are not available to proposer teams through any other resource. Accordingly, the following principles will apply to this solicitation.

(a) FFRDCs and government entities, including federal government employees, are not permitted to respond to this solicitation as a team member or subperformer on a proposed performer team.

(b) If an FFRDC or government entity has a unique research idea that is within the technology scope of this solicitation that they would like considered for funding; OR, if an FFRDC or government entity, including a federal government employee, is interested in working directly with the government team supporting the research described by this solicitation, contact CATALYST@arpa-h.gov.

(c) If a potential performer believes an FFRDC has a unique capability without which their solution is unachievable, they may provide documentation as part of their proposal submission demonstrating they have exhausted all other options. ARPA-H will consider the documentation to determine if inclusion of the FFRDC is necessary for the proposal.

4.3. Current Professional Support

Those currently providing support services[2] to ARPA-H to have an organizational conflict of interest (OCI) that cannot be mitigated and therefore are ineligible to propose.

4.4. Non-U.S. Organizations

[2] Support services are defined as contracted support providing technical, professional, financial expertise, and/or administrative assistance and may have access to internal and privileged information.

Non-U.S. entities may participate to the extent that such participants comply with any necessary non-disclosure agreements, security regulations, export control laws, and other governing statutes applicable under the circumstances. However, non-U.S. 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.

4.5 Proposer Teaming Structures

The CATALYST program is seeking unique teaming arrangements that are not the typical prime/subperformer arrangement. This program is a complex acquisition, and because of the different expertise required for varying phases and aspects of the program, and because there is a need for teams that can perform dynamically, it will virtually impossible that a single performer can perform all aspects of a program project. Additionally, because of the program approach, the expertise of different performers will be key at different stages of the program. Unlike a prime/subperformer arrangement where the prime performer is the leader of the team throughout, the teaming structure allows different members of the team to take the lead role at different stages of the program life cycle based on expertise and experience. The structure of a performing team and its teaming arrangement must be able to accommodate this type of change in project leadership over the course of performance, allow for open communication between the Government and all performers on a team, and ensure that all team members are responsible for performance and invested in the success of the program.

In the team structure, multiple individuals and/or organizations come together to work on a focused effort. All team members sign a teaming agreement, a contract signed by all members which identifies team members, roles, responsibilities, etc. The Government is not a party to this teaming agreement and will not assist or be involved the negotiation of the terms amongst the team members. This will be a private arrangement amongst the team members with no government dictated terms. Many teaming arrangements allow for members to leave the team during performance or for new members to join when needed but those options are at the discretion of the team members and what they are comfortable included as a collective. Team members have a wide range of options regarding how they establish and internally handle this relationship.

The multi-party team does **NOT** need to be established as a separate legal entity as the teaming agreement (also sometimes called articles of collaboration) is a contract serves to bind all members to the team. Should the team chose to incorporate or establish some form of legal entity, that is their choice but they should not feel that doing so or not will affect their selectability. The key point to understand is that it is the Government's desire to enter into an agreement with all of the team members that allows for direct interaction by the Government will all of the team members. For convenience the team generally choses one member to act as the agent and/or lead member who often handles administration duties on behalf of the team. For example, although the Government contract is between the multi-party team and the government, the agent will often sign the contract on behalf of the team. Additionally, the agent usually is also the direct payee, receiving funds from the Government and distributing payment to team members.

A multi-party team structure has many advantages over a typical prime/subperformer team. Because the team has chosen to work together in a collaborative manner, the teaming will be advantageous to all members and the alliance may even continue beyond the program. This team structure also gives the government privity of contract with all team members, allowing the government insight and visibility into all levels of technical and management actions, providing for direct communication for all team members with the government, ensuring that all team members are responsible for successful performance, and

enabling seamless leadership changes of the effort as the program project evolves.

4.5.1 Teaming Considerations

Ultimately, there are multiple ways to team and ARPA-H will not dictate the structure of the team, beyond the minimum requirements detailed below. At a minimum, the proposer teaming structure must:

1. Not be a prime/subperformer structure. Solution summaries/proposals submitted in this structure will be rejected as non-conforming. However, teams may subcontract with commercial vendors and consultants not performing an essential component of the program project.
2. Identify an organization to perform administrative functions and act as an agent for the team. The agent organization does not need to be the lead performing organization, but the agent must also perform substantive technical work on the program project beyond program management and administrative functions. Regardless, the Government must be free to interact with any team members not just the agent and/or lead performing organization.
3. Execute, prior to award, a teaming agreement that details the team structure, roles, and responsibilities and which binds the team members to the agreement. All members of the team must be parties to the other transaction. Whatever the team structure, the lead performing organization must be able to change during performance or between phases. The teaming agreement must account for the full scope of the CATALYST program. The Government is not a party to and will not approve the teaming agreement. The Government must have evidence that the teaming agreement has been executed in order to make an award to the team.
4. Include, as a minimum, one or more performing organizations for Phase I and a Phase II Product Sponsor. The Product Sponsor may join the team within the first year of performance, however, the preference is for the Product Sponsor to be identified and a signatory to the initial teaming agreement prior to award.

ARPA-H recognizes that this approach may be unfamiliar or new to many performers. ARPA-H strongly encourages performers who are interested in a deeper explanation of this approach and how it can be fully utilized by teams to attend the CATALYST Proposer's Day and ask any questions they may have.

4.6 Award Limitations

While there is statutory language that limits the number of awards ARPA-H may make to any one entity, that limitation does not necessary apply to all awards. Additionally, ARPA-H is prepared to waive the restriction in accordance with the statute where necessary/appropriate. ARPA-H encourages organizations to submit their research ideas notwithstanding the award limitation. Any proposal received will be fairly considered for award and, if it is of interest to ARPA H, may be selected for an award.

5. Submission Information

5.1. ISO Package

This announcement and any references to external websites herein constitute the total solicitation. If proposers cannot access the referenced material posted in the announcement found at https://www.sam.gov/, please contact the administrative contact listed herein.

5.2. Content and Form of Submission

NOTE: Non-conforming submissions that do not follow ISO instructions may be rejected without further

review at any stage of the process.

All submissions must be written in English with type not smaller than 12-point font (Arial or Times New Roman) and 1-inch margins. Smaller font may be used for figures, tables, and charts. Documents submitted must be clearly labeled with the ARPA-H ISO number, proposer organization, and proposal title/proposal short title.

5.2.1. Solution Summary Format

All solution summaries submitted in response to this ISO must comply with the content and formatting requirements in Appendix A. Solution summaries may not exceed four (4) pages, excluding the cover page and Rough Order of Magnitude (ROM). The Government will not review pages beyond four (4) pages. Official transmittal letter is not required.

Based on the evaluation of solution summaries, selected teams will be invited to submit full proposals.

5.2.2. Full Proposal Format

All proposals submitted in response to this ISO must comply with the content and formatting requirements in the applicable Bundle of Attachments templates. Proposers will use the templates provided in the Bundle of Attachments. The Bundle of Attachments includes the following seven proposal documents:

1. Technical and Management (35 pages)
2. Task Description Document (no page limit)
3. GANTT Chart Template (for Task Description Document)
4. Cost Proposal (no page limit)
5. Cost Proposal Spreadsheet (fill in applicable tabs)
6. Administration & National Policy (no page limit)
7. Model Agreement (Other Transaction)

Documents requested to be submitted with the templates should be included as attachments to the applicable template (e.g., HSR/ASR documents included as attachments to the Administration & National Policy template, cost back-up as attachments to the Cost Proposal template, etc.). Each template includes instructions for completion. Proposers must include an index for each attachment, excluding the cost proposal spreadsheet. An index does not count towards page limits, if applicable.

5.2.3. Administrative and National Policy Requirements

Proposers must complete the Administrative and National Policy Requirements document. Additional information regarding completion of the document is included below.

5.2.3.1. Organizational Conflicts of Interest

Proposers are required to identify and disclose all facts relevant to potential organizational conflicts of interest (OCI) involving a proposed team member, etc. Although the FAR does not apply to OTs, ARPA-H requires OCIs be addressed in the same manner prescribed in FAR subpart 9.5. Regardless of whether the proposer has identified potential OCIs under this section, the proposer is responsible for providing a disclosure with its proposal. The disclosure must include the proposer's and, as applicable, proposed team members' OCI mitigation plans, if necessary. The OCI mitigation plan(s) must include a description of the

actions the proposer has taken, or intends to take, to prevent the existence of conflicting roles that might bias the proposer's judgment and to prevent the proposer from having unfair competitive advantage. The OCI mitigation plan will specifically discuss the disclosed OCI in the context of each of the OCI limitations outlined in FAR 9.505-1 through FAR 9.505-4. The disclosure and mitigation plan(s) do not count toward the page limit.

5.2.3.1.1. Government Procedures

The Government will evaluate OCI mitigation plans to avoid, neutralize, or mitigate potential OCI issues before award and to determine whether it is in the Government's interest to grant a waiver. The Government will only evaluate OCI mitigation plans for proposals determined selectable under the ISO evaluation criteria and funding availability.

The Government may require proposers to provide additional information to assist the Government in evaluating the OCI mitigation plan.

If the Government determines a proposer failed to fully disclose an OCI; or failed to provide the affirmation of ARPA-H support as described above; or failed to reasonably provide additional information requested by the Government to assist in evaluating the proposer's OCI mitigation plan, the Government may reject the proposal and withdraw it from consideration for award or cancel award.

5.2.3.1.2. Agency Supplemental OCI Policy

In addition, ARPA-H restricts performers from concurrently providing professional support services, including Advisory and Assistance Services or similar support services, and being a technical performer. Therefore, as part of the FAR 9.5 disclosure requirement above, a proposer must affirm whether a proposed team member is providing professional support services to any ARPA-H office(s) under: (a) a current award or subaward; or (b) a past award or subaward that ended within one calendar year prior to the proposal's submission date.

If any professional support services are being or were provided to any ARPA-H office(s), the proposal must include:

- The name of the ARPA-H office receiving the support;
- The prime contract number;
- Identification of proposed team member, etc. providing the support; and

An OCI based on a performer currently providing professional support services, as described above, cannot be mitigated.

5.2.3.2. Research Security Disclosure

Proposers must submit and complete the Research Security Disclosure.

5.2.3.3. Intellectual Property (IP)

Proposers must provide a good faith representation that the proposer either owns or possesses the appropriate licensing rights to all intellectual property (IP) that will be utilized for the proposed effort. ARPA-H strongly encourages IP rights to be aligned with open-source regimes. Further, it is desired that all non-commercial software, software documentation, and technical data generated and/or developed under the proposed project is provided as a deliverable to the Government. IP delivered to the Government should

align with project or program goals and should be aligned with the level of Government funding provided to generate and/or develop the IP.

CATALYST will promote open-source data sharing in Phase I of the program, which is critical for model development, potentially spurring academia and industry to develop their own models. This could lead to wider adoption of computational model development and usage upon completion of the program. Data sharing (via ARPA-H approved open-source databases) and publication of the data and results will be a required deliverable in Phase I and Phase II of CATALYST. The performers may retain exclusive ownership of all IP for any developed products for commercialization during the CATALYST program.

Democratized access to the in silico simulation tools developed under this agreement is fundamental to the program and to the Government's goals for these agreements. The Government, therefore, will be looking to negotiate terms that provide for and guarantee continued access to the technology. This may include terms that allow the Government to grant licenses under certain circumstances and/or to have the performers grant licenses under certain circumstances. Performers should be prepared to negotiate and agree to such terms. Creative solutions are encouraged.

NOTE: IP rights assertions will be reviewed under Evaluation Criterion #1 stated in Section 6.1.

5.2.3.4. Human Subjects Research (HSR)

All entities submitting a proposal for funding that will involve engagement in human subjects research (as defined in 45 CFR § 46) must provide documentation of one or more current Assurance of Compliance with federal regulations for human subjects protection, including at least a Department of Health and Human Services (HHS), Office of Human Research Protection Federal Wide Assurance. All human subjects research must be reviewed and approved by an Institutional Review Board (IRB), as applicable under 45 CFR § 46 and/or. 21 CFR § 56. The entities human subjects research protocol must include a detailed description of the research plan, study population, risks and benefits of study participation, recruitment and consent process, data collection, and data analysis. Recipients of ARPA-H funding must comply with all applicable laws, regulations, and policies for the ARPA-H funded work. This includes, but is not limited to, laws, regulations, and policies regarding the conduct of human subjects research, such as the U.S. federal regulations protecting human subjects in research (e.g., 45 CFR § 46, 21 CFR § 50, § 56, § 312, § 812) and any other equivalent requirements of the applicable jurisdiction.

The informed consent document utilized in human subjects research funded by ARPA-H must comply with all applicable laws, regulations, and policies, including but not limited to U.S. federal regulations protecting human subjects in research (45 CFR § 46, and, as applicable, 21 CFR § 50). The protocol package submitted to the IRB must contain evidence of completion of appropriate human subjects research training by all investigators and key personnel who will be involved in the design or conduct of the ARPA-H funded human subjects research. Funding cannot be used toward human subjects research until all approvals are granted.

5.2.3.5. Animal Subjects Research (ASR)

Award recipients performing research, experimentation, or testing involving the use of animals shall comply with the laws, regulations, and policies on animal acquisition, transport, care, handling, and use as outlined in: (i) 9 CFR parts 1-4, U.S. Department of Agriculture rules that implement the Animal Welfare Act of 1966, as amended, (7 U.S.C. § 2131-2159); (ii) the Public Health Service Policy on Humane Care and Use of Laboratory Animals, which incorporates the "U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training," and "Guide for the Care and Use of

Laboratory Animals" (8th Edition)."

Proposers must complete and submit the Vertebrate Animal Section worksheet for all proposed research anticipating Animal Subject Research. A guide for completing the worksheet is in the hyperlink above.

All Animal Use Research must undergo review and approval by the local Institutional Animal Care Use Committee (IACUC) prior to incurring any costs related to the animal use research. For all proposed research anticipating animal use, proposals should briefly describe plans for IACUC review and approval. Funding cannot be used toward animal subjects research until all approvals are granted.

5.2.3.6. Controlled Unclassified Information (CUI) on Non-Federal Information Systems

Further information on Controlled Unclassified Information (CUI) identification, marking, protecting and control is incorporated herein and can be found at 32 CFR § 2002.

5.2.4. Submission Information

Submissions must be made to:

1. Solution summaries must be submitted to https://solutions.arpa-h.gov/
2. Proposals must be submitted to https://solutions.arpa-h.gov/Submit-Proposal/

Solution summaries and proposals must be submitted by the deadlines outlined in Part I., Overview Information.

A solution summary **must** be submitted prior to proposal submission. If encouraged, ARPA-H will request the proposer submit a full proposal after receiving ARPA-H solution summary feedback. A timeline for proposal submission will be provided to all proposers who submitted a solution summary, regardless of whether the solution summary was encouraged or discouraged.

NOTE: Submissions received after these dates and times will **not** be reviewed.

5.2.5 Proprietary Information

Proposers are responsible for clearly identifying proprietary information. Submissions containing proprietary information must have the cover page and each page containing such information clearly marked with a label such as "Proprietary." The government will protect any submissions marked as proprietary.

NOTE: "Confidential" is a classification marking used to control the dissemination of U.S. Government National Security Information as dictated in Executive Order 13526 and should not be used to identify proprietary business information.

5.3. Funding Restrictions

Pre-award costs will **not** be reimbursed unless a pre-award agreement is negotiated prior to award.

5.4. Questions

Interested entities may submit questions to the ISO Coordinator via the ISO mailbox CATALYST@arpa-h.gov. Answers to questions received will be posted to the same website. ARPA-H intends to post answers

to all relevant non-duplicative questions at intervals.

6. Solution Summary and Proposal Review Information

Solution summaries and proposals that are outside the scope of the ISO will not be evaluated further. In addition, solution summaries and proposals that do not meet the submission requirements or do not contain one or more of the required items listed above may be deemed non-conforming and will not be evaluated further.

ARPA-H will review eligible solution summaries and provide written feedback. At a minimum, feedback will encourage or discourage submission of a full proposal. Feedback will be sent to the administrative and technical points of contact noted on the solution summary cover page. Regardless of whether the Proposer is encouraged to submit a proposal in response to the ISO, it is eligible to do so. Solution summaries must be submitted in accordance with the requirements of Section 5.2.1 and solution summary feedback must be received prior to submission of a proposal.

Please note that although required to be submitted with the proposal, the Task Description Document for Other Transactions will not be evaluated as part of the proposal evaluation process.

6.1. Evaluation Criteria

Solution summaries will be evaluated based on Evaluation Criteria #1 and #2, in descending order of importance.

Full proposals will be evaluated using Evaluation Criteria #1-4, listed in descending order of importance.

6.1.1. Evaluation Criterion #1: Overall Scientific and Technical Merit

The proposed technical approach is innovative, feasible, and complete. Task descriptions and associated technical elements provided are complete and in a logical sequence with all proposed deliverables clearly defined such that a final outcome that achieves the goal can be expected as a result of award. The proposal identifies major technical risks and planned mitigation efforts are clearly defined and feasible. The proposal represents a revolutionary change rather than an incremental advance. In addition, the evaluation may take into consideration the extent to which the proposed IP rights and software components will potentially impact the ability to commercialize the technology.

6.1.2. Evaluation Criterion #2: Proposer's Capabilities and/or Related Experience

The proposed technical team has the expertise and experience to accomplish the proposed tasks. The proposer's prior experience in similar efforts clearly demonstrates an ability to deliver products that meet the proposed technical performance within the proposed budget and schedule. The proposed team has the expertise to manage the cost and schedule. Similar efforts completed/ongoing by the proposer in this area are fully described, including identification of other Government or commercial activities where they have led or participated. There will be evaluation emphasis given towards teams that include Product Sponsors (as defined in Section 2.3.1 and Section 2.3.2.4).

6.1.3. Evaluation Criterion #3: Proposer's Capabilities and/or Related Experience Potential Contribution and Relevance to the ARPA-H Mission

Potential future research and development, commercial, and/or clinical applications of the project proposed,

including whether such applications may have the potential to address areas of currently unmet needs within biomedicine and improve health outcomes. Degree to which the proposed project has the potential to transform biomedicine. Potential for the project to take an interdisciplinary approach.

6.1.4. Evaluation Criterion #4: Budget Risk Analysis

A budget risk analysis will be performed to assess costs proposed. This analysis may consider the overall affordability of the proposed project in context of the CATALYST program and ARPA-H. The analysis may also address discrepancies between the work proposed and the proposed cost for the project (e.g., costs that evince a lack of understanding of necessary resources) and innovative budget approaches that maximize project success. This is separate from the price reasonableness/value analysis that will be performed prior to award.

NOTE: Proposers are encouraged to propose the best technical solution. For example, proposers are discouraged from proposing low-risk ideas with minimum uncertainty or to staff the proposed effort with junior personnel to be more appealing from a budget perspective. ARPA-H seeks novel solutions that are reflective of the level of effort and risk proposed.

6.2. Review of Solution Summaries and Full Proposals

6.2.1. Review Process

It is ARPA-H policy to ensure impartial, equitable, comprehensive solution summary/proposal evaluations based on the evaluation criteria listed in Section 6.1. and to select the source(s) whose proposed solution that best meets the Government's technical, policy, and programmatic goals.

ARPA-H will conduct a scientific/technical review of each conforming solution summary/proposal. Conforming solution summaries/proposals comply with all requirements detailed in this ISO; solution summaries/proposals that fail to do so may be deemed non-conforming and may be removed from consideration. Solution summaries/proposals may be considered non-conforming if:

- The proposed concept does not fit within the program structure described in Section 2.
- The proposer did not meet the eligibility requirements.
- The proposal did not meet the submission requirements including registration in the System for Award Management (www.sam.gov).
- The proposal did not meet the content and formatting requirements.
- The proposer's concept has already received funding or been selected for award negotiations for another funding opportunity, whether from ARPA-H or another Government agency.

Please note that ARPA-H reserves the right, at its discretion, to reject as non-conforming solution summaries/proposals that it determines are substantially duplicative of previously submitted solution summaries, abstracts, and proposals under this or other ARPA-H solicitations. However, submissions under previous or current ARPA-H solicitations will not be automatically eliminated based on the same or similar solution proposed to another ARPA-H solicitation.

Solution summaries/proposals will not be evaluated against each other since they are not submitted in accordance with a common work statement.

Award(s) will be made to proposers whose solutions are determined to be the most advantageous to the Government, consistent with instructions and evaluation criteria specified in the ISO, considering price reasonableness and availability of funding.

6.2.2. Handling of Competition Sensitive Information

It is the policy of ARPA-H to protect all proposals as competition sensitive information and to disclose their contents only for the purpose of evaluation and only to screened personnel for authorized reasons, to the extent permitted under applicable laws. Restrictive notices notwithstanding, during the evaluation process, submissions may be handled by ARPA-H support contractors for administrative purposes and/or to assist with technical evaluation.

All ARPA-H support contractors are expressly prohibited from performing ARPA-H sponsored technical research and are bound by appropriate nondisclosure agreements. Input on technical aspects of the proposals may be solicited by ARPA-H from non-Government consultants/experts who are strictly bound by appropriate non-disclosure requirements. No submissions will be returned.

7. Award Administration Information

7.1. Selection Notices and Notifications

7.1.1. Solution Summaries

ARPA-H will respond to each responsive solution summary. At that time the proposer will be informed that:

1. ARPA-H does not encourage the proposer to submit a full proposal;
2. ARPA-H encourages the proposer to submit a full proposal;

Feedback will be provided to the administrative and technical points of contacts noted on the solution summary cover page.

Timelines for receipt of proposals will be provided to proposers as part of the request.

NOTE: ARPA-H will review all conforming full proposals using the published evaluation criteria and without regard to any comments resulting from the review of a solution summary.

7.1.2. Full Proposals

As soon as the evaluation of a full proposal is complete, the proposer will be notified that:

1. ARPA-H has not selected the proposal; or
2. ARPA-H has selected the proposal for funding pending award negotiations, in whole or in part. Official notifications will be sent via email to the Technical POC and/or Administrative POC identified on the proposal coversheet.
3. ARPA-H requires an explanation of any unclear elements in the submitted proposal. Based on that discussion, ARPA-H may not select the proposal or select the proposal in whole or in part and enter into negotiations.

Notification will be provided to the administrative and technical points of contacts noted on the proposal cover page.

7.2. Reporting

In addition to the reports noted above in the technical section, the number and types of reports will be

specified in the individual award document. As a typical model, ARPA-H expects the reporting will include monthly financial status reports, monthly technical status reports, a commercialization plan, a data management and sharing plan, and an end-of-phase report. The reports shall be prepared and submitted in accordance with the procedures contained in the award document and mutually agreed on before award. Reports and briefing material will also be required as appropriate to document progress in accomplishing program metrics. A final report that summarizes the project and tasks will be required at the conclusion of the performance period for the award, notwithstanding the fact that the research may be continued under a follow-on vehicle.

7.3. Electronic Systems

7.3.1. System for Award Management (SAM) and Unique Identifier Requirements

All proposers must have a valid Unique Entity ID (UEI) number and be registered in SAM, or have begun the SAM registration process, in order for their proposal to be found conforming. Proposers must maintain an active registration in SAM.gov with current information at all times during which a proposal is under consideration or have a current award with ARPA-H. Information on SAM.gov registration is available at SAM.gov.

NOTE: New registrations take an average of 7-10 business days to process in SAM.gov. Registration requires the following information:

- SAM UEI number
- Tax Identification Number (TIN)
- Commercial and Government Entity Code (CAGE) Code. If a proposer does not already have a CAGE code, one will be assigned during SAM registration.
- Electronic Funds Transfer information (e.g., proposer's bank account number, routing number, and bank phone or fax number).

7.3.2. i-Edison

The award document for each proposal selected for funding will contain a mandatory requirement for patent reports and notifications to be submitted electronically through i-Edison (https://www.nist.gov/iedisondison).

7.3.3 Section 508 of the Rehabilitation Act (29 U.S.C. § 749d)

All electronic and information technology acquired or created through this ISO must satisfy the accessibility requirements of Section 508 of the Rehabilitation Act (29 U.S.C. § 749d).

7.4. Agency Contacts

Points of Contact:
The ISO Coordinator for this effort may be reached at CATALYST@arpa-h.gov.

Collaborative efforts/teaming are encouraged. Interested parties should submit a one-page profile with their contact information, a brief description of their technical capabilities, and the desired expertise from other teams, as applicable. The CATALYST Teaming Profile Form may be found here: https://solutions.arpa-h.gov/Teaming/.

8. Other Information

ARPA-H will host a Proposers' Day in support of the CATALYST Program on the date listed in Part I., Overview Information of this ISO. The purpose is to provide potential proposers with information on the CATALYST program, promote additional discussion, and encourage team networking.

Interested proposers are not required to attend and any materials formally presented at Proposers' Day will be posted to SAM.gov.

ARPA-H will not reimburse potential proposers for participation at the Proposers' Day or time and effort related to submitting solution summaries/full proposals. To participate in the event, proposers must complete the online registration form located at: https://solutions.arpa-h.gov/CATALYST

Participants are required to register no later than the date listed in Part I., Overview Information of this ISO. This event is not open to the press. To facilitate easier access to underserved communities, Proposers' Day will be a hybrid event.

Appendix A: Solution Summary Template

Solution Summary Cover Letter
<TEAM LEAD ORGANIZATION LOGO (optional)>

Innovative Solutions Opening	
Solution Summary Title	
Team Lead Organization	
Type of Organization	**Choose all that apply:** Large Business, Small Disadvantaged Business, Other Small Business, HBCU, MI, Other Educational, or Other Nonprofit
Technical Point of Contact (POC)	Name: Mailing Address: Telephone: Email:
Administrative POC *(Authorized to Negotiate Award)*	Name: Mailing Address: Telephone: Email:
Total Basis of Estimate	Total: $
Place(s) of Performance	
Other Team Members (please indicate if they are team members or commercial vendors/consultants)	Technical POC Name: Organization: Organization Type:

NOTE: All submissions must be written in English with font type NOT smaller than 12-point font. Smaller font may be used for figures, tables, and charts. Delete all formatting and content instructions prior to submission. Content recommendations are displayed in blue font and should be deleted prior to solution summary submission. Solution summaries have a limit of four (4) pages. Citations do not count towards the four (4)-page limit.

Concept Summary
Clearly identify the applicable technical areas for the proposed CATALYST program project. Describe the solution summary concept with minimal jargon and explain how it addresses the applicable CATALYST technical areas.

Innovation and Impact
Clearly identify the outcome(s) sought and/or the problem(s) to be solved with the proposed technology concept. Describe how the proposed effort represents an innovative and potentially revolutionary solution to the applicable CATALYST technical areas. Explain the concept's potential to be disruptive compared to existing or emerging technologies and how the proposed approach will go far beyond current existing capabilities. To the extent possible, provide quantitative metrics in a table that compares the proposed technology concept to current and emerging technologies which may include:

- A progression of increasingly complex technical challenges.
- State of the art / emerging technology "baseline".
- Aggressive metrics in for each year of the proposed project.
- Summary of specific outcomes from the proposed research.

Proposed Work
Describe the final deliverable(s) for the project, key interim milestones, and the overall technical approach used to achieve project objectives. Discuss alternative approaches considered, if any, and why the proposed approach is most appropriate for the project objectives. Describe the background, theory, simulation, modeling, experimental data, or other sound engineering and scientific practices or principles that support the proposed approach. Provide specific examples of supporting data and/or appropriate citations to the scientific and technical literature. Identify adoption challenges to be overcome for the proposed technology to be successful. Describe why the proposed effort is a significant technical challenge and the key technical risks. At a minimum, the solution summary should address:

- Does the approach require one or more entirely new technical developments to succeed?
- How will technical risk be mitigated?
- What use cases, capabilities, or demonstrations will be featured?

Team Organization and Capabilities
Indicate the roles and responsibilities of the organizations and key personnel that comprise the project team. Provide the name, position, and institution of each key team member and describe in 1-2 sentences the skills and experience they bring to the team.

Separately, please complete the below table for key personnel on a separate page of the solution summary. The table does not count towards the page limit but must not exceed one page.

Organization	Last Name	First Name	City	State	Country

Basis of Estimate (BOE)
Please include a BOE of timeline and federal funds requested, as well as the total project cost including cost sharing, if applicable. The BOE should also include a breakdown of the work by direct labor (fully-burdened), labor hours, vendors/consultants, materials, equipment, other direct costs (e.g., travel), profit, cost sharing, and any other relevant costs. The below table may be used for this breakdown:

Categories	**Amount**
Direct Labor (fully-burdened)	
Labor hours	
Vendors/Consultants	
Materials	
Equipment	
Travel	
Other Direct Costs	
Profit	
Total	
Cost Sharing (if applicable/appropriate)	