THIS IS A DRAFT MODULE ANNOUNCEMENT. SEE SECTION 8 AND 9, BELOW, OF THIS MODULE ANNOUNCEMENT FOR DIRECTIONS REGARDING THE QUESTION AND ANSWER PROCESS. THIS IS NOT AN INVITATION FOR PROPOSALS. ANY SUCH RESPONSE WILL BE DISREGARDED.

DRAFT MODULE ANNOUNCEMENT

FOR

ADVANCED RESEARCH PROJECTS AGENCY FOR HEALTH

DECENTRALIZED ENGINEERING OF CELLS INFORMED BY DYNAMIC EVIDENCE (DECIDE) EXPLORATION TOPIC

ARPA-H-MAI-24-01-07

AUGUST 20, 2024

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MODULE ANNOUNCEMENT OVERVIEW INFORMATION

FEDERAL AGENCY NAME: Advanced Research Projects Agency for Health (ARPA-H)

MODULE ANNOUNCEMENT TITLE: Decentralized Engineering of Cells Informed by Dynamic Evidence (DECIDE)

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ANNOUNCEMENT TYPE: Initial Announcement

MODULE ANNOUNCEMENT NUMBER: ARPA-H-MAI-24-01-07

DATES:

- *Module Announcement Draft release date*: August 20, 2024
- *Questions & Answers (Q&A) due date*: October 4, 2024
- *Moduledue da Announcement release date*: TBD
- *Proposal due date*: October 22, 2024.

1. RSO EXPLORATION TOPICS

A. INTRODUCTION

ARPA-H is launching an Exploration Topic that aims to enable pediatric patients with rare genetic diseases to access clinically validated curative cell therapies by advancing novel quality assurance mechanisms at Academic Medical Centers (AMC). This ET expands the Resilient System Office's (RSO) funding approach associated with the interest areas included within Appendix A to the Master Announcement Instructions, ARPA-H-MAI-24-01. Exploration Topics will be announced via Module Announcements issued under the Master Announcement Instructions (MAI), ARPA-H-MAI-24-01. Exploration Topics are short-duration, fast-paced efforts with smaller, targeted awards. Each Exploration Topic will pursue topics that strategically align with the RSO mission and provide foundational proofs-of-concept for additional future research to be built upon.

B. EXPLORATION TOPIC STRUCTURE, AWARD VALUE, AND PROPOSAL INFORMATION

Exploration Topic, or ETs, will describe short-duration, fast paced efforts that are no more than 24 months in duration. ETs may consist of a single base period or may consist of multiple stages. Stage structure will be defined in each ET module announcement. Regardless of structure, the total duration of each topic is not anticipated to exceed 24 months. Specific technical objectives to be achieved, task descriptions, intellectual property rights, milestone payment schedule, and deliverables will be included in each ET module announcement.

Proposals identified for negotiation will result in negotiating an award of an Other Transaction (OT) Agreement. Use of an OT Agreement provides significant opportunities for flexible execution and arrangements given the nature of the work to be conducted under these ETs and assists in meeting RSO's aggressive research goals. Moreover, all resulting ET module announcements will result in OT Agreements with fixed payable milestones. Fixed payable milestones are fixed payments based on the successful completion of the milestone accomplishments agreed to in the milestone plan. Specific milestones will be based upon the ET objectives stipulated in each ET module announcement (see Section D, "Exploration Topic Structure, Schedule and Milestones" of the ET module announcement).

Additionally, ETs allow for a streamlined solicitation and acquisition approach. ARPA-H is looking to finalize a new award within 60 days of selection notification letters being sent out. Accordingly, proposers must review the model OT Agreement provided in Attachment 1 of each

ET module announcement prior to submitting a proposal. ARPA-H has provided the model OT to expedite the negotiation and award process and to ensure ARPA-H achieves the goal of finalizing awards within 60 days of selection notification letters being sent. The model OT is representative of the terms and conditions that ARPA-H intends to include in ET module announcement awards. All Stage 1 submissions under the ET (see Section 6.A below) must include the model OT Agreement, if the proposer IS suggesting minimal edits.[1] The submission must include proposed edits utilizing revision markings and must include a comment explaining the concern the proposed change addresses. However, ARPA-H may not accept suggested edits. A proposer does not have to provide a model OT agreement in the Stage 1 submission if edits are NOT being proposed. If an edited version of the model OT is not provided as part of the proposal package, ARPA-H assumes that the proposer has reviewed and accepted the award terms and conditions, indicating agreement (in principle) with the listed terms and conditions applicable to the specific award instrument. The proposer should, in this instance, ensure the Administrative & National Policy Requirements document clearly denotes agreement with the listed terms and conditions. The Government also reserves the right to remove a proposal from award consideration should the parties fail to reach an agreement on OT award terms and conditions within the award timeline stipulated above.

3. OPPORTUNITY DESCRIPTION

The mission of the Advanced Research Projects Agency for-Health (ARPA-H) is to accelerate better health outcomes for everyone by advancing innovative research that addresses society's most challenging health problems. Awardees will develop groundbreaking new ways to tackle health-related challenges through high potential, high-impact biomedical and health research. ARPA-H seeks proposals to develop breakthrough technical approaches to identify, quantify, and mitigate sources of production variability across decentralized, small batch manufacturing of autologous cell therapies. The Decentralized Engineering of Cells Informed by Dynamic Evidence (DECIDE) ET endeavors to produce tools and technology that enable accelerated evaluation and validation of Good Manufacturing Practices (GMP) for small batch therapies by demonstrating product quality and consistency that is commensurate with the amount of therapy that needs to be produced. By creating quantitative method(s) to dynamically inform the number of required batches, DECIDE seeks to ensure access to critical therapeutic solutions for Americans and provide a revolutionary pathway to address market failures by innovating approaches to right-size cell therapy production for pediatric rare disease.

A. EXPLORATION TOPIC INTRODUCTION

The DECIDE Exploration Topic (ET) aims to enable pediatric patients with rare genetic diseases to access clinically validated curative cell therapies by advancing novel quality assurance technologies and pathways at Academic Medical Centers (AMC). Significant investment from AMCs has led to the creation of life-altering therapies for children suffering from these rare diseases. However, access remains limited due to non-medical barriers such as the lack of technological innovation to right-size cell therapy production, the absence of methods to

[1] This deviates from the proposal preparation instructions included within Section 3.1 of the MAI, ARPA-H-MAI-24-01.

robustly validate the quality and consistency of these therapies, and lack of automated evidence collection mechanisms that can enable novel coverage and reimbursement pathways. This effort will right-size the production of cell therapies for pediatric populations with rare diseases, innovate methods to streamline the commercial GMP validation process, and create a pathway to commercial sustainability for rare disease therapies created at non-traditional locations. By addressing these barriers, DECIDE will enhance the accessibility of these critical therapies to children with rare diseases across the United States.

Autologous cell therapy, which uses a patient's own cells as the biological starting material before modifying their molecular properties for therapeutic use, represents a personalized approach that has historically resulted in costly manufacturing and approval processes. This economic challenge has led companies to abandon cell therapies for rare diseases due to unsustainable business models despite robust clinical efficacy. In some cases, companies have even returned licenses to academic institutions, forcing them to financially support these million-dollar therapies themselves.[2] DECIDE aims to build an effective and navigable ecosystem for academic centers to economically produce and administer autologous cell therapies for rare diseases through technological innovations that would unlock the possibility for regulatory advancements, and coverage/reimbursement pathways.

To achieve this, DECIDE aims to develop breakthrough technologies to identify and quantify sources and impacts of production variability across decentralized, small batch production of autologous cell therapies. DECIDE will then pair these technologies with models to dynamically inform the criteria for assessing batch quality and consistency. Together, these novel tools will enable a streamlined and cost-effective regulatory approval process that aligns with the scale of production for small-batch autologous cell therapies. This will reduce the financial burden on AMCs and incentivize the development of therapies for rare diseases. Developed technologies and methodologies will be accessible to industry stakeholders and made generalizable and adaptable to various autologous cell manufacturing systems, allowing AMCs to adopt and implement these innovations without significant additional costs or resources.
By aligning quality assurance processes in hospital and academic settings with regulatory expectations, ARPA-H can de-risk its growing investment in revolutionary therapies and provide an end-to-end solution that enables the production of long-lasting and potentially curative interventions at lower costs and in a manner that automates evidence collection for regulatory and reimbursement pathways. Critically, this effort will proceed in strong partnership with Food and Drug Administration's (FDA) Center for Biologics Evaluation and Research (CBER/FDA), the National Institute of Standards and Technology (NIST), and the Center for Medicare and Medicaid Services (CMS).

National Health Impact

[2] Jensen. "Orchard abandons promising gene therapy for rare immune disorder." (2021).

In 2024, nearly 1,000 cell therapy clinical trials were underway in the U.S., demonstrating the growing interest and immense potential in this burgeoning area of medical research. Underlying this surge in research are advancements in genetic modification technologies (e.g., CRISPR, viral vectors, etc.) that enable the precise and/or permanent modification of DNA, opening the door to treating rare genetic diseases. There are over 7,000 identified rare diseases (diseases affecting less than 200,000 individuals), with 72% of them having a genetic basis and 70% beginning in childhood.[3] The direct and indirect costs of these diseases carry a U.S. economic burden of nearly $1 trillion every year.[4] Currently, only 5% of rare diseases have FDA approved treatments, an unmet need that emerging cell therapies are aiming to address. Though cell therapies are increasingly demonstrating therapeutic safety and efficacy, patients are often unable to access them. An example use case arose in Artemis-deficient severe combined immunodeficiency (SCID) which, although rare in the general population (1 in 65,000 births), has a high incidence among persons of Navajo or Apache descent (1 in 2000 live births) and in certain related populations.[5,6] To treat this rare genetic disease, clinicians in a U.S.-based AMC received investigational new drug approval and successfully engineered gene corrected autologous CD34+ cells capable of reconstituting the immune system in Native American children.[7] Though the science and technology to treat these children exists, Navajo and Apache children face substantial obstacles in accessing the treatment they require due to the extreme rarity of their condition. Despite robustly demonstrating clinical effectiveness, the AMC is unable to cost-effectively meet the current manufacturing requirements to obtain the FDA designation that would qualify the treatment for reimbursement. Thus, all manufacturing must be performed with philanthropic funding, which is an unsustainable model that does not provide children access to this life-saving treatment. On average, the AMC estimates each treatment to cost about $500,000 (cost of goods and services only). To date, 13 children have been treated. Based on the remaining philanthropic funding, only 1-2 more children will be able to receive treatment, leaving several dozen untreated.

The innovations developed through the DECIDE ET could be applied to a wide range of rare genetic diseases beyond Artemis-deficient SCID, including other severe combined immunodeficiency (SCID) disorders (e.g., X-linked SCID and ADA-SCID) alpha-thalassemia major, metachromatic leukodystrophy, recessive dystrophic epidermolysis bullosa, leukocyte adhesion deficiency-1, Wiskott-Aldrich syndrome, adrenoleukodystrophy, and numerous other ultra-rare diseases for which there are no FDA approved commercial treatments.

B. EXPLORATION TOPIC STRUCTURE AND INTEGRATION

DECIDE is a twenty-four (24) month, three-stage Exploration Topic with a single Technical Area (TA). DECIDE will develop novel technical approaches to identify and quantify sources and impacts of production variability across decentralized, small batch manufacturing of autologous cell therapies with the goal of dynamically inform decision criteria for confidently assessing the

[3] The Lancet Diabetes & Endocrinology "Rare diseases: individually rare, collectively common." (2023).
[4] Yang et al. "The national economic burden of rare disease in the United States in 2019." (2022).
[5] Amatuni et al. "Newborn Screening for Severe Combined Immunodeficiency and T-cell Lymphopenia in California, 2010-2017." (2019).
[6] Li et al. "A Founder Mutation in Artemis, an SNM1-Like Protein, Causes SCID in Athabascan-Speaking Native Americans." (2002).
[7] Cowan et al. "Lentiviral Gene Therapy for Artemis-Deficient SCID." (2022).

quality of batches manufactured in low volume for rare therapies.

Stage I: Method development

In Stage I, performers will simulate small batch manufacturing processes and materials to identify sources of variability. Concurrently, performers will develop statistical methods to support risk-adjusted decision making that scale with the intended number of commercial doses to be manufactured. Six months into the ET, an Independent Verification and Validation (IV&V) will assess variability detection and attribution methods along with the statistical methods that will inform minimum batch quantity.

Stage II: Testing and prototyping

In Stage II, performers will identify unique signatures associated with distinct causes of variation and develop a signature library across sites. In parallel, performers will apply and refine statistical methods into decision support tools for regulators to assess cell production quality and consistency. Fifteen months into the ET, IV&V will verify signature correlation with underlying variability sources and will assess tool capabilities against FDA feedback and requirements.

Stage III: Deployment and validation

In Stage III, performers will apply variability signatures across sites and/or within different contexts to validate that the variability signatures allow them to correct for the source of variation in subsequent production batches. Performers will also test and validate their decision support tools on real data sets for new cell therapies.

Process Variation Modeling & Dynamic Decision Support Tools

The DECIDE ET will pursue innovation within a single TA to confidently assess the quality of batches manufactured at AMCs in low volumes for rare therapies. This initiative aims to make curative cell therapies for rare diseases more accessible to patients by reducing the costs associated with commercial-equivalent GMP validation while maintaining high standards across critical quality attributes. The primary objectives are: (1) optimize the consistency of decentralized small batch autologous cell production by identifying sources of manufacturing variability, and (2) to develop methodologies that dynamically inform decision criteria for assessing batch quality and consistency. By attributing batch variations to underlying causes, such as patient cells or components of the manufacturing process, this TA aims to generate evidence that would enable dynamic evaluation and approval criteria that right-size the number of doses to be produced while maintaining rigorous quality and efficacy standards.

To translate variation attribution data into actionable tools to assist regulatory decision-making, performers will develop quantitative method(s) to dynamically inform the number of required batches based on the quantity of intended therapy recipients. This will enable cell therapies for rare diseases to achieve more favorable economies of scale, thereby dramatically reducing manufacturing cost and time to bring curative therapies to patients. By integrating predictive

analytics into the manufacturing workflow, the program aims to establish a robust decision-making framework that ensures each batch adheres to necessary standards while optimizing resource allocation and minimizing production costs.

Objective 1: Optimize the consistency of decentralized small batch autologous cell production by identifying sources of manufacturing variability. Variability refers to the inherent difference or fluctuations that can occur in the properties, behavior, or quality attributes of cells produced during a given manufacturing process, impacting the consistency and reliability of the final cell product. Achieving this goal will require innovating new approaches for performing variability attribution analyses that leverage a range of input data across the autologous cell manufacturing processes and developing methodologies to confidently determine the optimal level of manufacturing validation necessary for curative, small batch, therapies.

To address this TA, performers will identify potential sources of manufacturing variability by operating within a pre-defined autologous cell manufacturing system(s), with performer-specified features including cell modification approach(es), equipment types, and system setups. Performers will acquire data from samples, using novel technologies or existing tools, that are representative of the full range of possible conditions and scenarios for their given system and source material, including noisy samples and failure mechanisms, with the goal of attributing batch variability to specific sources. Data may include but is not limited to single-cell multi-omics (e.g., transcriptomics), imaging-based assays (e.g., phenotypic classification), or retrospective data from prior pre-clinical or clinical studies.

Prior to Stage I, performers will enter the ET with a rare disease(s) of interest. Diseases may include but are not limited to SCD disorders, sickle cell disease, metachromatic leukodystrophy, recessive dystrophic epidermolysis bullosa, leukocyte adhesion deficiency-1, Wiskott-Aldrich syndrome, and adrenoleukodystrophy. The DECIDE ET will focus on specific cell therapies that will be pursued as products. Performers will also enter the ET with an established autologous cell manufacturing process(es) with pre-defined equipment and steps, including but not limited to modification approach (e.g., viral vector), targeted cell type (e.g., haemopoietic stem cells), and quality control assays. In Stage I, performers will develop methods that simulate the underlying manufacturing processes or components (e.g., reagent quality, contamination at various manufacturing stages, human error, etc.) that could allow for a systematic and precise study of manufacturing variability and attribution to causative sources. Simulations may include a combination of *in silico* and *in vitro* studies. Additionally, performers are encouraged to incorporate systems, components, and/or processes that would make decentralized, small batch autologous cell manufacturing more accessible and affordable. For example, using automated or semi-automated systems and/or testing reagents that are more widely available and not beholden to single vendors. Resulting technologies and methodologies will also be designed in a way that could be used by the wider cell therapy community for more efficiently and accurately identifying and verifying variability across diverse manufacturing systems.

In Stage II, performers will use novel technologies and methods, alongside data from Stage I, to identify specific markers (i.e., signatures) that correlate with variation in key quality attributes. Signatures are genotypic or phenotypic features that are associated with variation observed in the cell manufacturing process with statistical significance. For example, the way a patient's illness progresses (i.e., source variability) could significantly affect the structure of cellular

membranes (i.e. phenotypic signature), which can be detected through optical, chemical, or molecular techniques (i.e., signature measurement). The association of signatures with sources of variation in manufacturing processes will enable more efficient identification of variability in the cell manufacturing process. The signatures and associated methodologies will serve as a foundation for future innovations, especially in the area of Process Analytical Technology (PAT) for small batch autologous cell manufacturing.

In Stage III, performers will apply variability signatures across at least two sites to validate improvements to decentralized manufacturing. By testing in multiple locations, performers will demonstrate the ability to reliably identify and quantify production variability within different contexts.

Objective 2: Dynamically inform decision criteria for assessing batch quality and consistency. In parallel with identifying and attributing sources of variability in decentralized cell therapy production, performers will innovate and demonstrate new statistical approaches to support risk-adjusted decision making that scale with the intended number of commercial doses to be manufactured. In Stage I, performers will develop statistical methods that will quantitatively inform the minimum number of batches to confidently ensure quality consistency for rare and/or low volume therapies. In Stage II, performers will apply and refine these statistical methods into a tool that supports regulators in confidently navigating specific decisions necessary to determine the quality and consistency of small batch and/or decentralized cell production. Statistical decision support tools and the underlying methods will be transparent and explainable, such that regulatory bodies can confidently assess their validity. In Stage III, performers will test their tools on real data sets for new cell therapies.

The development and application of these advanced decision support tools would enable regulators to scale the validation requirements to the scale of intended production (e.g., number of productions batches required to assess quality consistency), thereby ensuring that high quality standards are met without imposing barriers that could inadvertently hinder clinically validated cell therapies from reaching patient populations.

The combination of innovations for each objective will result in dramatic improvements in manufacturing efficiency and ability for clinically validated therapies to reach patients. By enabling attribution of variation in manufactured cell products, regulators can quickly determine if the variability is cause for concern, and manufacturers can rapidly address the root cause of the variation in the manufacturing process. The data sharing component inherent in this TA would unlock a pathway to widespread decentralized manufacturing of small batch cell therapies, dramatically improving the resilience and accessibility of the cell therapy landscape. Finally, the decision support tool(s) and underlying explainable statistical methods would reduce barriers to rapid regulatory approval of clinically validated therapies by enabling evaluators to confidently scale the requirements for expensive validation of production consistency based on the number of therapies being produced.

See section 6A for proposal preparation instructions and topics deemed out of scope for the DECIDE ET.

C. Exploration Topic Metrics

The metrics are expressed in terms of targets and are indicated as being set at a particular time after the beginning of the program. These targets are expected to vary between individual performer groups depending on the sampled microbial data, health outcomes, and modeling techniques. The final definition of these targets will be subject to the Program Manager's approval at the indicated program checkpoints. However, proposers are encouraged to state the expected range of achievable values for metrics labeled as "Set accuracy target" or "Set target" to illustrate the expected performance capabilities of the proposed models.

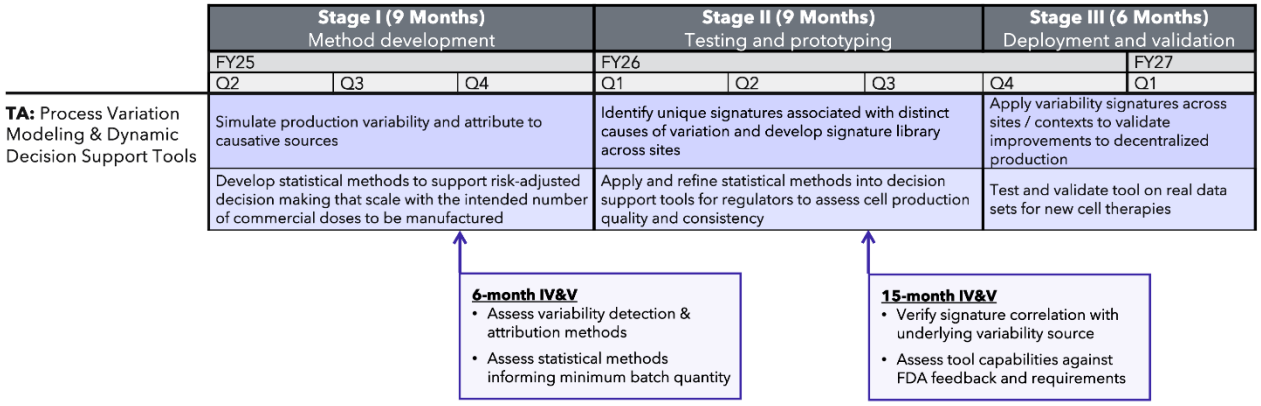
Figure 1. DECIDE ET metrics

	Stage I	**Stage II**	**Stage III**
Metric	End of 9 months	End of 18 months	End of 24 months
Simulation coverage (Percentage of the manufacturing process steps able to be replicated via *in silico* or *in vitro* simulations)	70%	80%	95%
Variability attribution (Percentage of variability in the manufacturing process that can be attributed to specific root cause(s) within and/or across production sites)	20%	35%	50%
Signature definition (Percentage of identified variability sources that have correlating signatures defined)	60%	80%	90%
Tool useability (average Likert score [1-10 scale] for decision support tool usability)	≥ 7	≥ 7	≥ 9
Tool maturity (technology readiness level #)	≥ 1	≥ 2	≥ 3

D. Exploration Topic Structure, Schedule, and Milestones

DECIDE is a 24-month ET comprised of three Stages that will require performers to efficiently allocate resources in developing capabilities described in this ET. Proposals must address the requirements of each Stage of the ET. See Section 6.A for the module category associated with the DECIDE ET. Figure 2 below illustrates the DECIDE ET Timeline and Key Milestones. Timeframes are relative to the start of the effort.

Figure 2: DECIDE ET Timeline and Key Milestones



Proposers must address the DECIDE ET objectives, metrics (Figure 1), and the following fixed payable milestone deliverables in their proposals (Figure 3). The task structure should be consistent across the proposed schedule, Task Description Document (TDD), the Stage 1, Volume 1 Basis of Estimate, and if selected for a potential award, the Stage 2, Volume 2 Price/Cost proposal. Proposers must use the Task Description Document (TDD) template provided within Attachment 1 of the DECIDE ET module announcement. The TDD will be Attachment 1 of the resulting OT Agreement.

If selected for award negotiation, the fixed payable milestones provided will be directly incorporated into Attachment 3 of the OT Agreement ("Agreement Term, Deliverables, and Payment Schedule" of the model OT) with milestone amounts calculated based on the proposed accumulation of monthly amounts up to each milestone date.

Fixed milestones for this project must include at a minimum, the following:

Figure 3. DECIDE ET fixed payable milestone deliverables

Milestone #	Milestone & Exit Criteria	Milestone / Deliverable	Expected Due Date*
Stage I:			
1	Report on simulation methodologies, describing initial execution and preliminary results of variability source attribution. When available, describe the impact of variability on critical quality attributes. Document IRB protocol approval for all work, as/if necessary. Note that this report may be shared with FDA partners for review.	Variability Report #1	Month 3
2	Report on intermediate simulation developments including identified sources of variability and plans for further development. When available, describe the impact of variability on critical quality attributes. Participate in an IV&V third-party assessment.	Variability Report #2	Month 6

	Note that this report may be shared with FDA partners for review.		
3	Report final variability metrics, as well as provide a comprehensive list of sources of variability and their respective impact on the product's critical quality attributes. Develop a signature identification plan, informed by simulation and variability attribution results. Plans should describe data acquisition and analysis tools and methodologies. Note that this report may be shared with FDA partners for review.	Final Variability Report Signature Identification Plan	Month 9
Stage II:			
4	Report on signature identification methodologies, describing initial execution and preliminary results. Note that this report may be shared with FDA partners for review.	Signature Report	Month 12
5	Report intermediate signature results including the signatures accuracy and strength, as well as next steps for further development. Participate in an IV&V third-party assessment. Note that this report may be shared with FDA partners for review.	Signature Report #2	Month 15
6	Report final signature metrics for Stage II, as well as provide a comprehensive list of identified signatures and how they could be used for verifying batch consistency. If applicable, describe how signatures could be translated into novel technologies (e.g., process analytical technologies) for cell manufacturing. Develop a statistical modeling plan, informed by simulation and variability attribution results, and signature identification. Plans should describe modeling methodologies and validation approaches. This report will be shared with FDA partners. Clearly indicate how the identified signatures that could be used for verifying batch consistency align with current FDA GMP guidance to preserve clinical integrity, quality, and variability.	Final Signature Report Statistical Modeling Plan	Month 18
Stage III:			
7	Report on statistical modeling approaches, describing initial execution and preliminary results.	Statistical Modeling Report	Month 21

	Note that this report may be shared with FDA partners for review.		
8	Report on the final summarized technical findings from the Exploration Topic, demonstrating Stage III metrics, and including opportunities for continuing to advance the technology and its application and outstanding challenges. This finalized report will be shared with FDA partners. Clearly indicate how the summarized technical findings align with current FDA guidance. If applicable, provide suggested updates to FDA guidance, supported by your technical findings, and describe how these updates preserve clinical integrity, quality, and variability to maintain FDA GMP objectives.	Final Technical Report	Month 24

**Months after award*

Performer Reviews and Program Manager Meetings:

The DECIDE Exploration Topic will require performers to participate in regularly scheduled meetings for progress updates. The following meetings are anticipated:

- Annual review meetings (in person) convening all performing teams across the exploration topic (locations TBD).
- Annual "site visits" (in person) with the ARPA-H team traveling to performer research facilities and/or building sampling facilities (staggered every other 6-month period with the review meetings)
- Quarterly review meetings (virtual) between each performer team, the ARPA-H team, and collaborating agencies / organizations.

Independent Verification and Validation (IV&V):

Six months into the DECIDE ET, independent entities partnering with ARPA-H will assess variability detection and attribution methods along with the statistical methods that will inform minimum batch quantity. At six months into Stage II (15 months into the ET), IV&V partners will verify signature correlation with underlying variability sources and will assess tool capabilities against FDA feedback and requirements. Performers will also test and validate their decision support tools on real data sets for new cell therapies. Performers are expected to collaborate with these IV&V partners throughout the ET's duration.

E. Policy Conformance, Agile Development, Open Standards, and Intellectual Property

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

- Common IT Security Configurations

- Federal information technology directives and policies
- Section 508 of the Rehabilitation Act of 1973 (29 USC 794d) as amended by P.L. 105-220 under Title IV (Rehabilitation Act Amendments of 1998)
- HHS OCIO Policy for Information Technology (IT) Enterprise Performance Life Cycle (EPLC)

In concert with ARPA-H and partners, proposers should address innovative solutions to design, architect, develop, and test the technologies described in the DECIDE ET.

Proposers must provide a good faith representation that the proposer either owns or possesses the appropriate licensing rights to all intellectual property that will be utilized for the proposed effort. Proposers should appropriately identify any desired restrictions on the Government's use of any Intellectual Property contemplated under the award instrument in question. This includes both noncommercial items and commercial items. Respondents should utilize the prescribed format within the Administrative & National Policy Requirements Document Template (Attachment 1, OT Bundle) when asserting restrictions. If no restrictions are intended, then the proposal should state "NONE."

F. Health Data Protection and Privacy

- Proposers must present within the proposal submission a data acquisition, collection, and management plan for how health data will be sourced and preserved while ensuring the integrity of the data collected throughout the period of performance.
- Health data that will be collected by Performers in the DECIDE ET will remain confidential and not be subject to secondary analysis or sharing without the explicit consent of the health data owner.
- DECIDE ET program deliverables MUST not include raw health data (e.g. names and other identifying information). Performers must de-identify the health data to be included within any program deliverable.
- Sharing of any program information and/or program deliverables will be controlled and in accordance with the negotiated terms of the resulting Agreement. Program information will be shared during the period of performance, within the DECIDE Government team (e.g. the IV&V team and other key Government stakeholders).
- The associated Intellectual Property rights for all program deliverables will be negotiated with each selected Performer prior to Agreement award. Program information will be controlled in accordance with the Agreement, and all DECIDE deliverables will be appropriately marked as negotiated by the Performer and ARPA-H.

G. Electronic invoicing and payments

See Section 5.2.6 of the MAI, ARPA-H-MAI-24-01.

4. AWARD INFORMATION

Multiple awards are anticipated under this announcement; however, the number of proposals selected for award will depend on the quality of the proposals received and the availability of funds.

See Section 1.4 of the MAI, ARPA-H-MAI-24-01 for additional information on award information.

5. ELIGIBILITY

See Section 2 of the MAI, ARPA-H-MAI-24-01 for eligibility requirements.

6. MODULE ANNOUNCEMENT RESPONSES

A. PROPOSAL PREPARATION INSTRUCTIONS

(a) All proposal submissions must be written in English with Avenir Next LT Pro Light font type not smaller than 11-point. Smaller font may be used for figures, tables, and charts. Content and formatting are disclosed in the OT Bundle (Attachment 1). Below is the page restriction for each Module category applicable to this ET:

- BYTE Module is > $2,000,000 ≤ $5,000,000: Volume 1 shall be limited to 15 pages.
- KILO Module is > $5,000,000 ≤ $10,000,000: Volume 1 shall be limited to 20 pages.

Performers can apply for BYTE or KILO Module. While the Government anticipates the abovementioned Module categories, the below not to exceed estimates per Stage are provided to aid in preparation of proposal submissions:

Stage I should not exceed $3,000,000.
Stage II should not exceed $3,000,000.
Stage III should not exceed $2,100,000.

NOTE: Proposals should select a cost point that is commensurate with the scale and complexity of the proposed approach. Proposals that simply align a proposed budget to the Module Category ceiling value are strongly discouraged. Thus, if a proposal is selected for Stage 2 submissions and the basis of estimate was simply aligned to the Module Category ceiling value, the Government will require a full cost proposal (i.e., direct and indirect rates, labor hours, equipment, material, other direct costs, etc.) that must be substantiated by salary documentation, indirect rate agreements, material and equipment quotations and a justification for proposed labor categories and hours that correlates directly to the proposed Task Description Document. The submission of a full cost volume will impact Stage 2 price/cost proposal timelines and will likely be followed by extensive cost negotiations.

(b) All proposal submissions must address all metrics, objectives, Stages, and substages in proposal submissions.

(c) Proposals should address the following:

i. Decentralized Small Batch Autologous Cell Production

- What manufacturing process will you use for small batch autologous cell production? Describe one or more well-defined small batch autologous cell manufacturing process(es) from cell retrieval through cell modification to quality control testing. Processes should include, but are not limited to equipment and reagents, modification approach (e.g., viral vector), cell types, and quality control assays. Strong proposals will describe cell manufacturing processes that focus on stem cells (e.g., hematopoietic stem cells) while other cell types may be considered if justified by compelling reasons. Additionally, strong proposals will describe the use of lentiviral vectors while other delivery vehicles and mechanisms may be considered if justified by compelling reasons. Proposals must describe manufacturing processes that could be used for treating/curing ultra-rare pediatric diseases (i.e. <100 patients per year).
- What efficacy data do you have for the aforementioned manufacturing process? Provide data (pre-clinical and/or clinical data) that sufficiently demonstrates the efficacy of the outlined manufacturing process. Sufficient data does not involve the vast quantity of data required for FDA approval but should instead definitively show that the described manufacturing process can produce cells with clearly defined critical quality attributes.
- How will the outputs of the DECIDE ET be tested across multiple sites? Provide a detailed plan for applying variability signatures across decentralized sites that will be used to validate improvements to decentralized manufacturing. Plans should involve at least two sites with a preference for more than two sites. Strong proposals will include a letter of support from each site to show that the proposer has the necessary relationships/collaborations across multiple sites.

ii. Variability Attribution

- What is your current understanding of where variability originates within your manufacturing process? Provide an overview of current data showing where variability enters the pre-defined manufacturing process, impact of the variability (e.g., reduced product potency), what methods are used to identify and measure that variability, and where gaps and limitations in understanding and quantifying variability exists.
- How would you simulate small batch autologous cell manufacturing? Describe methods for simulating the aforementioned small batch autologous cell manufacturing process(es), which may involve *in silico* methods or wet lab experimentation. Proposers are encouraged to utilize a combination of in silico and wet lab experimentation to cover at least 95% of the manufacturing process by the end of the DECIDE ET. Describe the cost-effectiveness of the proposed

simulation strategy, considering the cost of reagents and the necessary types of data to gather.

- How will simulations contribute to a deeper understanding of where variability originates? Provide a detailed plan for introducing variability into manufacturing simulations. Strong proposals will describe approaches for expanding the breadth of variability sources (e.g., simulating human error and different pieces of equipment), maximizing generalizability (e.g., simulating commonly used processes, steps, and/or equipment), and promoting resiliency (e.g., simulating bench-top manufacturing or reagents that are more easily accessible rather than customized to specific pieces of equipment).
- How would you distinguish different types of variation? Proposals should describe methods that will distinguish meaningful variation (e.g. impacting CQAs) from variation that results from measurement error, insufficient data, or abstractions when converting the real world into quantitative measurements.

iii. Signature Identification

- How would you link variation to specific signatures? Describe strategies for identifying specific markers (i.e., signatures) that correlate with variation arising within a cell manufacturing process. When possible, provide detailed evidence for the precision and strength of signature identification technologies and methodologies.
- How would signature identification lead to improved cell manufacturing processes? Describe how novel signatures could eventually help correct the source of variation quickly to reduce the number of manufacturing runs necessary to reach a desired product quality.

iv. Decision Support Tool

- How can statistical approaches be used to inform the number of small batches produced? Explain new or existing statistical approaches to support risk-adjusted decision making that scale with the intended number of commercial doses to be manufactured.
- How could the final output of the DECIDE ET be used by the FDA to aid decision making? Describe how these statistical methods could be applied and refined into a tool that supports regulators in confidently navigating specific decisions necessary to determine the quality and consistency of small batch and/or decentralized cell production. Strong proposals will describe how statistical methods will be used to build a statistical decision support tool that is transparent and explainable, such that regulatory bodies can confidently assess their validity. Strong proposals will describe a tool that is adaptable, or could be eventually modified or expanded upon, to a range of small batch autologous cell manufacturing processes.

(d) The following is considered out of scope for the DECIDE ET:

i. Proposed approaches should not include specific reagents, methods, or other cell therapy components that will be submitted for IND approval or that are in clinical trials. For example, proposers should not propose the use of a specific lentivirus and cell type that in combination comprise a specific autologous cell therapy that is currently in a clinical trial.

B. Proposal Content and Format

This Module Announcement is soliciting Stage 1 Volume 1 proposals in accordance with the staged submission and evaluation process referenced in Section 3.1 and 4.1 of ARPA-H-MAI-24-01. Reference to Stages in this section of the DECIDE ET module announcement is not to be confused with the programmatic Stages of the DECIDE ET described above.

Stage 1 Volume 1 proposals must contain the following document submissions:

- TECHNICAL & MANAGEMENT
- BASIS OF ESTIMATE (BOE)
- TASK DESCRIPTION DOCUMENT
- ADMINISTRATIVE & NATIONAL POLICY REQUIREMENTS
- MODEL OT AGREEMENT (ONLY IF PROPOSING EDITS)

Note: page restrictions apply ONLY to the Technical & Management section Stage 1, Volume 1 submission. All proposals submitted in response to this announcement must comply with the content and formatting requirements of the OT Bundle (Attachment 1). Proposers are strongly encouraged to use the templates provided in the OT Bundle associated with this announcement. Information not explicitly requested in the MAI, this announcement, or OT Bundle, may not be evaluated.

If a Stage 1 proposal is selected for potential award, a proposer will be notified by the Government and required to submit a Stage 2 price/cost proposal for further consideration (see Section 3.1 and 4.1 of ARPA-H-MAI-24-01).

EQUITY REQUIREMENTS

ARPA-H is committed to equitable health care access irrespective of race, ethnicity, gender/gender identity, sexual orientation, disability, geography, employment, insurance, and socioeconomic status. To that end, in considering health outcome data and potential applications of the MoBE health index, proposers are encouraged to consider health equity and ensure that all populations can benefit from the outcomes of this ET.

C. Proposal Submission Instructions

Proposal submission should be submitted to https://solutions.arpa-h.gov/Submit-Proposal/. Submission via any other method will be disregarded.

Proposers should consider the submission time zone and that some parts of the submission process may take from one business day to one month to complete (e.g., registering for a SAM Unique Entity ID (UEI) number or Tax Identification Number (TIN); see Section 5.2.1 of the MAI for information on obtaining a UEI and TIN).

D. Proposal Due Date and Time

Proposals in response to this notice are due no later than 12:00 PM Eastern Daylight time (EDT) on October 22, 2024. Full proposal packages as described in Section 6.A must be submitted per the instructions outlined in this module announcement and received by ARPA-H no later than the above time and date. Proposals received after this time and date will not be reviewed.

Proposers are warned that the proposal deadline outlined in the DECIDE ET will be strictly enforced. When planning a response to this notice, proposers should consider that some parts of the submission process may take from one business day to one month to complete.

7. PROPOSAL EVALUATION AND SELECTION

Proposals will be selected and evaluated in accordance with Section 4 of the MAI, ARPA-H-MAI-24-01, through Amendment 1. The Government reserves the right to decide which performers, if any, are selected for the award.

8. ADMINISTRATIVE AND NATIONAL POLICY REQUIREMENTS

Section 5.2 of the MAI, ARPA-H-MAI-24-01 provides information on Administrative and National Policy Requirements that may be applicable for proposal submission as well as performance under an award.

9. POINT OF CONTACT INFORMATION

DECIDE ET Module Announcement questions should be directed to:
https://solutions.arpa-h.gov/Ask-A-Question
ATTN: ARPA-H-MAI-24-01-06

10. QUESTIONS & ANSWERS (Q&As)

All questions regarding this notice must be submitted to the link noted in Section 9. Emails sent directly to the Program Manager, or any other address will be **discarded**.

All questions must be in English. ARPA-H will attempt to answer questions in a timely manner. Questions should be submitted by October 4, 2024, for full consideration. Questions submitted after that date may not be answered.

In concert with this Announcement, ARPA-H will post Q&As for the DECIDE ET Module Announcement on the ARPA-H webpage under News & Events. ARPA-H encourages all proposers to review the Q&As provided before submitting additional questions to the

respective link noted in Section 9. The Government may not answer repetitive questions already answered in the posted Q&As.