



INNOVATIVE SOLUTIONS OPENING
FOR
EMERGING
HEALTH
INNOVATORS
EHI

OFFICE OF COMMERCIALIZATION
ARPA-H-SOL-26-150

September 15, 2026

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ATTACHMENT A: Solution Summary Template

ATTACHMENT B: Pitch Slides Template

ATTACHMENT C: Technical and Management Proposal Template

ATTACHMENT D: Task Description Document (TDD)

ATTACHMENT E: Milestone Payment Schedule Template

ATTACHMENT F: Administrative and National Policy Requirements Document Template

ATTACHMENT G: ARPA-H Model Other Transaction (Provided for reference purposes only)

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

PROGRAM TITLE: Emerging Health Innovators (EHI) Initiative

ANNOUNCEMENT TYPE: Solicitation

ISO SOLICITATION NUMBER: ARPA-H-SOL-26-150

DATES: (All times listed are Eastern Time)

- **Solution Summaries Due:** October 30, 2026, 2:00 PM ET
- **Questions & Answers (Q&A) due date:** February 3, 2027, 2:00 PM ET
- **Full Proposals Due:** February 10, 2027, 2:00 PM ET
- **Tentative Performer Selection Date:** April 30, 2027
- **Tentative Award Start Date:** June 30, 2027

ANTICIPATED AWARDS: Multiple Other Transaction (OT) Agreements

AWARD AMOUNT: Each award consists of the following periods of performance and not to exceed (NTE) values. Total Award Value shall not exceed \$1,050,000:

- Base Period Year 1 (12 Months): \$350,000 (NTE)
- Base Period Year 2 (12 Months): \$350,000 (NTE)
- Option Period Year 3 (12 Months): \$350,000 (NTE)

AGENCY CONTACT: All inquiries should be sent to EHI2026@ARPA-H.gov

1. ISO PURPOSE

ARPA-H seeks proposals from all eligible entities (see Section 2.6 Eligibility Information) to accomplish the EHI Program goals as described in this solicitation package. Ultimately, ARPA-H intends to negotiate multiple OT Agreements with proposers whose proposals are most advantageous to the Government.

1.1 ISO QUESTIONS AND ANSWERS (Q&A)

All questions regarding this Innovative Solutions Opening (ISO) must be submitted to EHI2026@ARPA-H.gov. ARPA-H will post Q&As to the ARPA-H EHI webpage on an ongoing basis and will not respond directly to email inquiries. All questions should be in English and must include the name, email address, telephone number of a point of contact, and should be submitted by the Q&A deadline posted with other key dates. Do not submit questions to individual Government team members.

ARPA-H will attempt to answer questions in a timely manner; however, questions submitted after the due date may not be answered. Further, duplicative questions may be combined and rephrased to streamline responses.

1.2 DEFINITIONS

Several important terms used within this solicitation are defined below:

- Early-Career Investigator – An individual within 8 years of completing their first terminal degree who is eligible to serve as Project Lead (leaves of absence, post-doctoral, residency, and fellowship periods can be excluded for determination of eligibility). Post-doctoral fellows/trainees and clinical trainees do not qualify as Early-Career Investigators for purposes of serving as Project Lead but may participate as support staff.
- Key Member – An individual identified in the proposal (including the project lead and any other named personnel, whether employed by the proposer or a subawardee/consultant) whose expertise or role is critical to executing the Task Description Document (TDD).
- Proposer – A “proposer” is the *organization* responding to this ISO. Proposers must have a unique entity identifier (UEI) and be registered in SAM.gov to submit a response to this ISO.
- Project Lead – The “project lead” is the *individual* representative from the proposer’s organization who leads the project’s progress and success.
- Selectee – After a proposer is selected for negotiation of a potential award, they are considered a “selectee.”
- Performer – After a selectee’s agreement has been awarded, they are considered a “performer.”
- Topic Area (TA) – Indicates one of the multiple technical submission pathways within the EHI Initiative. Proposers will only be permitted to respond to one TA.

2. THE INITIATIVE

2.1 EHI OVERVIEW

Initiative Overview: The EHI Initiative will ensure ARPA-H identifies and engages early career investigators. To achieve this goal, ARPA-H is soliciting proposals from these researchers and innovators and their organizations to develop cutting-edge biomedical, health, and community-engaged research and innovation.

This ISO solicits proposals that must identify one eligible Project Lead/PI for research and development in the specific TAs identified in Section 2.3. Teams may include collaborators, subawardees and consultants. Potential applicants are encouraged to carefully consider the descriptions of the TAs before submission. Applicants may not submit to multiple TAs and will be required to choose one TA for a solution summary or proposal submission and identify this TA on the submission’s cover sheet. A submission may be determined to be non-conforming if the solution summaries or proposal does not clearly address a specific TA or an applicant submits more than one solution summary or proposal for consideration. ARPA-H reserves the right to assign a solution summary or proposal to a different topic area than indicated by the proposer.

Prior to submitting a proposal, applicants are required to first submit a solution summary. After reviewing a solution summary, ARPA-H will notify the proposer only of a determination to either “encourage” or “discourage” submission of a full proposal. No additional feedback – written

or verbal – will be provided at this stage. The project lead should be a researcher, not an administrator, who meets eligibility criteria as defined in Section 2.6.1.

2.2 INITIATIVE STRUCTURE, TIMELINE AND TOPICS

The EHI program initiative is a mentorship program that seeks to identify and engage with early-career individuals so they can learn about ARPA-H's approach to addressing gaps in health care in the United States while seeding new and innovative research ideas. The EHI program will fund innovative research proposals across diverse technical areas of interest to ARPA-H. Further details regarding the specific technical areas of interest are in Section 2.3.

Proposals must cover a 24-month base period and for all research activity. Each proposal must include a plan for an additional 12-month option period called the "Director's Award". This optional period will be reserved for a limited number of performers who demonstrate exceptional EHI project performance over the 24-month base period.

The EHI program contains multiple TAs. Proposed research should investigate innovative approaches that enable revolutionary advances in science, devices, or systems. Specifically excluded is research that primarily results in evolutionary improvements to the existing state of practice.

2.3 TOPIC AREAS

Topic 1: Precision Control of Skin Inflammation without Systemic Exposure

Autoimmune and inflammatory skin diseases (e.g., psoriasis, systemic sclerosis) affect over 7 million Americans and drive approximately \$150B in annual healthcare costs, with major pain, disfigurement, disability, and systemic comorbidities. Current care relies on topical agents and systemic immunomodulators or biologics that are imprecise, require chronic use, and can cause serious adverse effects. Management is episodic and reactive, with no continuous sensing of local immune status. No existing technology provides intelligent, persistent skin-surface biosensor networks that sense cutaneous inflammation and autonomously modulate therapy while preventing systemic exposure. These limitations constrain precise, surface-level, adaptive control of skin inflammation and perpetuate reliance on systemic immunosuppression.

ARPA-H seeks bold, cross-disciplinary solutions that integrate biomaterials, AI/swarm networking, and immunomodulation to enable precise, surface-level, adaptive control of skin inflammation without systemic immunosuppression. ARPA-H is particularly interested in networked, non-internalizable biomaterials that reside in superficial skin layers, self-organize to sense cutaneous inflammation, share data, and deliver localized treatment or defer treatment when systemic risk is high. Concepts that exclude systemic, lymphatic, and neural uptake while enabling distributed sensing, computation, and reversible therapy confined to the skin are especially encouraged.

Proposed concepts may encompass innovations in techniques, platforms, and/or integrated technologies that:

- Achieve persistent, surface-level biosensing of local immune status across superficial skin layers, with validated exclusion from systemic, lymphatic, and neural compartments
- Enable self-organizing network behavior among distributed biomaterial elements to share data, perform local computation, and coordinate reversible, localized therapy
- Establish treatment logic that delivers localized intervention during inflammatory flares or defers therapy when systemic risk is high, tailored to specific cutaneous autoimmune and inflammatory indications (e.g., psoriasis, systemic sclerosis)

Concepts should be supported by clear experimental or computational strategies to demonstrate feasibility and rigor, such as:

- Platform demonstrations with validated systemic exclusion and core sensing/networking functions in early phases
- Integrated prototypes with defined performance in relevant preclinical models at mid-program milestones
- Rigorous safety/biocompatibility assays, independent validation, and robust encryption/cybersecurity testing of network logic

Robust metrics for technical performance (e.g., sensing accuracy, network stability, systemic safety, treatment efficacy, biocompatibility), impact, operability (including ease of application/removal, comfort, and integration into dermatology workflows), cost and manufacturability for out-patient and home use, and commercialization potential are expected.

Topic 2: Internal Sensing and Targeted Control of Inflammation

Inflammatory diseases affect over 100 million Americans and cost hundreds of billions of dollars annually. Current anti-inflammatory therapies are imprecise, can cause systemic toxicity even for localized disease, and require repeat clinical visits. Care is reactive and based on intermittent data, with major gaps in internal real-time inflammatory sensing, coordination of multi-site inflammation via injectable or ingestible platforms, and micro-/nano-scale closed-loop or externally controlled therapy. As a result, millions of patients continue to receive whole-body drugs that cause significant side effects, while inflammation at its source remains poorly characterized and inadequately controlled.

ARPA-H seeks cross-disciplinary solutions that integrate nanotechnology, immunomodulation, and AI/swarm networking to enable precise, autonomous inflammation control that treats disease at its source while sparing healthy tissue. We are particularly interested in injectable or ingestible micro/nano-scale networked platforms that reside in the body, sense inflammation, and deliver targeted therapy under external or closed-loop control. Concepts that leverage biocompatible micro/nanoparticles for tissue-targeted platforms, miniaturized inflammatory biosensors, swarm-inspired signaling protocols, and externally triggered or closed-loop drug delivery are especially encouraged.

Proposed concepts may encompass innovations in techniques, platforms, and/or integrated technologies that:

- Achieve internal, real-time sensing of inflammation via injectable or ingestible micro/nano-scale platforms with validated biocompatibility and durability
- Enable cross-tissue communication and coordination across multi-site inflammation through swarm signaling and/or externally controlled therapy with validated safety
- Establish closed-loop or externally triggered drug delivery with overrides and fail-safes, tunable to specific inflammatory conditions and anatomical sites

Concepts should be supported by clear experimental and computational strategies to demonstrate feasibility and rigor, such as:

- Platform demonstrations with validated systemic exclusion and core sensing/networking functions in early phases
- Integrated prototypes with defined performance in relevant preclinical models at mid-program milestones
- Simulation-guided, iterative *in vivo* testing, parallel materials evaluation, and rigorous preclinical safety studies

Robust metrics for technical performance (e.g., sensing accuracy, cross-tissue communication fidelity, biocompatibility, durability, safe degradation/clearance, therapeutic efficacy), impact, operability (including delivery via standard injection or ingestion for use in primary care and rural settings), cost and manufacturability benchmarked against biologics, and commercialization potential are expected.

Topic 3: Deep Brain Stimulation for Mechanistic Sleep Exploration (Deep Sleep)

Sleep is a critical driver of cognition, mental health, and overall physiological resilience, yet most human sleep research is constrained to superficial measures such as scalp electroencephalogram (EEG), wearables, and subjective reports. These approaches provide only coarse views of neural dynamics and offer limited insight into how deep-brain circuits orchestrate and modulate sleep quality. As a result, the mechanisms linking specific deep-brain activity patterns during sleep to physical health, mental health, and neurodegeneration remain poorly understood, and opportunities for precise, circuit-level interventions are largely unexplored.

Implantable deep brain stimulation (DBS) technologies offer the potential to directly sense and perturb neural activity in deep structures during sleep. DBS systems provide an opportunity to both monitor and modulate deep brain structures and circuits to identify intracranial biomarkers of sleep-wake dynamics and advance therapeutic innovations for improving sleep quality.

ARPA-H is interested in understanding activity in deep brain circuits during sleep with the aim of unlocking new treatments to optimize sleep quality. This topic seeks approaches that leverage DBS technologies to: (1) measure and characterize deep brain electrophysiological activity that control arousal and sleep-wake dynamics; (2) quantify how these signals correlate with superficial cortical activity and other physiological markers; (3) establish causal relationships via targeted, closed-loop modulation during sleep; and/or (4) advance novel closed-loop, personalized interventions that modulate the deep brain circuits of arousal and sleep.

Topic 4: CLEAR-MIND – Restoring the Brain’s Drainage and Immune Balance to Enable Healing After Injury

The brain glymphatic system and the immune system play key roles in resolving damage to the brain due to trauma, surgery, or other insults. The immune system can be suppressed, either chronically (e.g. patients with organ transplants, auto-immunity, etc.) or acutely (e.g. to control inflammation during surgery or after other forms of injury). This immune suppression, however, can be counterproductive by interfering with glymphatic function in the brain, which is essential for healing.

This topic seeks to develop interventions that restore the brain’s natural drainage and rebalance its immune response after injury, so that the effects of the initial insult are not exacerbated. ARPA-H is interested in treating these two systems – drainage and immunity – as something that can be measured and restored, rather than left to fail. Proposers are encouraged to show, in preclinical models, that re-establishing the brain’s drainage and calming the harmful aspects of its immune response leads to measurable improvements in outcome.

This is a hard, cross-disciplinary problem that no single field or company is positioned to solve alone. It requires bringing together experts in the brain’s vascular and lymphatic systems, the immune system, imaging, and targeted therapeutic delivery. A central challenge is timing: the brain’s immune cells can be both helpful and harmful at different times post-injury, so any intervention must be delivered in the right window. Proposers are encouraged to address this timing directly and to use imaging that can track drainage and inflammation over time.

Given the level of effort, this topic is scoped as a mechanistic feasibility effort, not a cure. The goal is to prove that drainage can be restored in the context of immune system modulation, shifting the immune response toward repair, and providing real signs of improved outcomes – packaged as a go/no-go evidence base for a larger program. Restoring function for the millions living with brain-injury disability is the long-term vision; this effort takes the first rigorous step. It is well-suited to an early-career investigator working across brain science, immunology, and bioengineering.

Performers will be asked 1) to demonstrate a model of immune suppression that worsens glymphatic function and outcomes in response to brain damage (year 1); 2) identify target pathways for intervention (year 2); and 3) test selected interventions (year 3).

Quantifiable objectives (24-month feasibility):

- Restore $\geq 50\%$ of normal brain drainage (measured by imaging) after injury in a preclinical model undergoing immune suppression
- Demonstrate a measurable shift in immune cells from a damaging to a repair-supporting state
- Achieve a $\geq 30\%$ reduction in injury and inflammation markers versus untreated controls

- Deliver a go/no-go evidence package linking restored drainage and immune balance to improved outcomes

Topic 5: Host-Pathway Interventions for Neurotropic Disease (HIND)

Neurotropic pathogens such as rabies virus and Eastern equine encephalitis virus along with prion-associated disorders remain extraordinarily difficult to treat once neurologic symptoms emerge. In many cases, pathogen-directed strategies, such as monoclonal antibodies, are too slow, incomplete, or biologically insufficient to prevent progressive CNS injury after disease is clinically apparent. As a result, patients often face irreversible neurologic decline, with few or no options beyond supportive care.

ARPA-H is interested in research concepts that address the central problem of whether late-stage neurotropic disease can still be therapeutically altered by interrupting host or host-pathogen processes that drive ongoing pathology after CNS involvement. Relevant processes may include maladaptive neuroimmune activation, neuronal injury or degeneration programs, barrier dysfunction, synaptic or circuit destabilization, metabolic failure, proteostatic collapse, or other disease-amplifying host responses.

Projects should focus on clinically relevant symptomatic stages and seek to determine whether manipulation of these processes can preserve neurologic function, slow disease progression, or improve survival even when direct clearance of the underlying agent is delayed, incomplete, or not feasible. Concepts that define actionable windows for intervention, demonstrate benefit in realistic late-stage models, and reveal convergent mechanisms across distinct neurotropic diseases are strongly encouraged. Technical focus areas:

- Identify reversible host-driven mechanisms of neurologic injury in late-stage disease;
 - Focus on mechanisms that continue to drive CNS damage after symptoms begin.
- Discover biomarkers linked to disease progression, intervention opportunities, and predictive outcomes;
 - Test whether modulating host or host-pathogen processes can preserve neurologic function, slow progression, or improve survival even when pathogen clearance is incomplete
- Develop clinically relevant models, delivery methods, and outcome measures.
 - Use realistic late-stage disease systems to evaluate novel CNS delivery of medical countermeasures and measure meaningful functional rescue and survival outcomes.

ARPA-H is particularly interested in research concepts that address discovery of critical metabolic and proteomic biomarkers linked to host-pathogen interactions, novel delivery methods of medical countermeasures (MCMs) - specifically effective against late-stage neurotropic diseases - to the central nervous system, determination of clinically relevant treatment windows based upon molecular biomarker signatures, and measurable molecular features linked to clinically relevant outcomes are strongly encouraged.

Relevant references:

- <https://www.pnas.org/doi/10.1073/pnas.1308817110>
- <https://www.mdpi.com/1999-4915/11/2/192>
- <https://journals.asm.org/doi/10.1128/jvi.01323-08>
- <https://www.frontiersin.org/journals/microbiology/articles/10.3389/fmicb.2020.561530/full>
- <https://www.nature.com/articles/s42255-022-00652-3>
- <https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2025.1578202/full>

Topic 6: Protecting Patient Data in Life Science AI

The rapid development and implementation of large language models (LLMs), biological design tools (BDTs), and other foundation models in life sciences are driving ideation, discovery, and clinical care for industry and healthcare. At the same time these systems introduce new risks when trained on sensitive clinical, genomic, molecular, imaging, and/or longitudinal health data. Recent publications have demonstrated that these models may unintentionally memorize and expose patient-linked information, enable discovery of specific patient's data use for training, and/or remain vulnerable to prompt injection and other data extraction methods. While many of these vulnerabilities have been demonstrated on models in other fields, in life science models these concerns may be amplified because datasets often contain rare disease profiles, unique genomic signatures, data from the same patient shared across models, familial-linked data, and multimodal patient records that are difficult to fully de-identify.

ARPA-H seeks proposals that define and measure patient data privacy risks in life science AI while developing practical tools that help model developers reduce those risks without slowing innovation. These efforts should address challenges beyond simply screening, obfuscating, and/or removing known PII (Personal Identifiable Information) in training data. Examples of potential research topics are below:

- Characterizing and defending against membership inference and model inversion in models trained on clinical, biological sequence, and structural data;
- Developing tools to measure data leakage and memorization in biological and patient-linked training datasets;
- Advancing scalable and provable machine unlearning methods so that sensitive records or data classes can be removed effectively from trained models;
- Creating automated evaluation pipelines and scorecards to baseline newly released models for privacy, robustness, and extraction risk;
- Securing agentic AI systems that connect models to biomedical design, clinical workflows, or clinical environments;
- Methods uniquely suited for securing biological and clinical models from distillation attacks.

Research concepts which address multi-modal types of clinical and biological data – from imaging to genomics – are strongly encouraged.

ARPA-H is particularly interested in platforms that:

- Create common baselines for trusted model release, enabling developers, health systems, and biotechnology organizations to compare privacy and extraction risk across models, modalities, and use cases.
- Support secure data reuse across the bioeconomy, allowing sensitive clinical, genomic, molecular, imaging, and longitudinal datasets to advance innovation while reducing the risk that patient-linked information is exposed.

Relevant references:

- <https://www.nature.com/articles/s41586-026-10688-0>
- <https://pmc.ncbi.nlm.nih.gov/articles/PMC12680930/>
- <https://www.mdpi.com/1660-4601/20/15/6539>
- <https://dl.acm.org/doi/full/10.1145/3523273>
- <https://ieeexplore.ieee.org/document/9833649>
- <https://openreview.net/pdf?id=BpAx3OuNOr>
- <https://dl.acm.org/doi/abs/10.1145/3460120.3484756>

Topic 7: Engineering DRT for Programmable DNA Synthesis as Emerging New Medical Countermeasures (MCM) Strategy

Recent discoveries in bacterial phage immunity pathways have identified defense-associated reverse transcriptases (DRTs) – which naturally confer protection against phages through cDNA synthesis – as the first known biological system to challenge the last unbroken paradigm of the Central Dogma – protein to RNA to DNA. Two recent studies have shown that DRTs mediate protein-templated synthesis of sequence-specific concatemeric dinucleotide DNA. Notably, DRT3b was shown to synthesize a protein-primed poly(AC) strand in the absence of a nucleic acid template. These findings, together with emerging structural data, create an opportunity to systematically interrogate microbial sequence databases for related systems and to drive molecular engineering of DRTs for more precise and programmable DNA synthesis.

DRTs may also have substantial translational potential across multiple elements of health and disease. As components of bacterial immune defense, preliminary studies suggest possible antibiotic-free antimicrobial therapeutic applications, including direct induction of bacterial cell death and novel strategies to optimize phage libraries. In addition, the distinctive structural interactions between DRTs and their target proteins may enable new classes of detection platforms for protein-specific targets, including toxins and small-molecule pharmaceuticals. The future translational space for DRTs are well aligned with ARPA-H's mission and may create a completely novel line of therapeutics and diagnostics for human health. Examples of potential concepts include:

- Pursue bioengineering and synthetic biology approaches to reprogram DRT protein, enabling synthesized DNA motifs beyond current natural limitations;

- Identify DRT regulatory mechanisms that can be leveraged for adaptive and precise read-write control of functional DNA products both intracellularly and in vitro;
- Explore DRT-linked apoptosis pathways to drive novel antimicrobial countermeasures strategy, especially against species resistant to traditional antibiotics;
- Investigate prokaryotic conservation of DRT protein-templated DNA synthesis paradigm and the breadth of conserved functions shared across prokaryotes for human-relevant biological control.

ARPA-H is particularly interested in platforms that:

- Enable programmable novel therapeutic or countermeasure modalities by exploiting DRT functions in microbial defense systems, including investigating their adaptability to mammalian systems and their potential to address urgent public health and national health security needs.
- Explore novel diagnostic, sensing, and other biochemical functions enabled by DRT protein-templated DNA synthesis that could accelerate therapeutic development.
- Generate foundational structural datasets and design rules for non-nucleic acid-templated DNA synthesis to advance predictive structural modeling.

References:

- <https://www.science.org/doi/10.1126/science.aed1656>
- <https://www.science.org/doi/10.1126/science.adq0876>
- <https://www.science.org/content/article/scientists-stunned-fundamentally-new-way-life-produces-dna>
- <https://www.frontiersin.org/journals/microbiology/articles/10.3389/fmicb.2026.1866040/full>

Topic 8: Prevention of Lethal Alpha-gal Allergic Responses Caused by Tick Bites

Alpha-gal syndrome (AGS) is an increasingly recognized severe allergic condition caused by tick bite-induced sensitization to galactose-alpha-1,3-galactose (alpha-gal). Subsequent exposures to alpha-gal found in consumed red meat, dairy, or certain medications can trigger delayed, severe allergic responses making it challenging to immediately identify the source of exposure, resulting in missed diagnoses of AGS and increased risk of future exposures and life-threatening allergic reactions. Meanwhile, there are no clear diagnostic tools to predict AGS or interventions for patients with AGS beyond prevention of future tick exposures, strict avoidance of red meat, dairy, and select alpha-gal-containing medications. ARPA-H seeks to create comprehensive immune mapping of tick exposure to elucidate the cellular and molecular pathways driving severe AGS.

ARPA-H seeks R&D approaches to identify and functionally map of tick-bite associated innate and adaptive immune responses that induce allergy, inflammation, and the transmission of tick-borne diseases. These efforts will leverage immune profiling to better understand tick-bite-induced host sensitization mechanisms and longitudinal disease trajectories.

Examples of potential concepts include:

- Longitudinal cellular and serological immune profiling of alpha-gal exposed individuals to support the discovery of novel clinical biomarkers of AGS and to develop AGS risk-scores for exposed patients.
- Comprehensive biochemical analyses, including glycolipid profiling of Lone Star tick saliva and bite transmission studies, to identify the molecular source and mechanisms of alpha-gal-induced allergy in humans.
- Comprehensive human allergy immune atlas following tick bite exposure to identify immune targets that could dampen or reduce allergic responses to alpha-gal.

Proposed concepts may encompass innovations in techniques, platforms, and/or integrated technologies that:

- Develop deep multi-omic characterization of tick saliva allergens that drive anti-alpha gal IgE sensitization in asymptomatic and symptomatic AGS patients.
- Develop platforms to assess the dynamics of the innate and adaptive immune systems from tick saliva exposure and tick bite-associated disruption of epithelial integrity, and to define how these responses contribute to the development and severity of AGS.
- Develop a scalable immunological mapping and clinical biomarker platform to rapidly identify recently exposed patients at highest risk of developing severe alpha-gal syndrome.
- Develop novel AGS treatment and prevention strategies to eliminate future tick bites and transmitted tickborne diseases.

Topic 9: SMILE (Smart Microbiome-Informed Lesion & Enamel restoration)

Dental caries (including tooth decay or cavities) are one of the most common chronic health conditions in the United States. More than 90% of adults and 46% of youth have untreated tooth decay, with disproportionate impact among the 1.7 million rural Americans living in “dental deserts” without reliable access to dentists and the quarter of adults (72 million) who lack dental insurance. The health implications of tooth decay extend far beyond oral health, significantly increasing risk of and worsening existing chronic conditions, such as heart disease, diabetes, respiratory inflammation, and brain disorders. Treatment of dental caries relies on in-office procedures to remove decayed tissue and subsequently protect healthy tissue with synthetic materials such as composite resin, amalgam, or ceramic. While these materials are durable, fillings typically need to be replaced every 5-10 years. Despite widespread adoption of oral hygiene practices that prevent dental caries, many patients experience recurrent caries despite good oral hygiene due to genetic factors associated with weaker enamel and oral microbiome imbalances that promote acid-producing bacteria. These challenges underscore the need for a fundamentally new approach that is biologically informed, minimally invasive, durable, and accessible outside of clinical settings.

ARPA-H is interested in bold, interdisciplinary approaches that leverage recent advances in bio-inspired materials science and oral microbiome research to transform how dental caries are detected and treated. This topic seeks to develop microbiome-aware diagnostics and smart materials capable of repairing early-stage tooth decay prior to the onset of irreversible tissue loss.

Proposers are encouraged to explore solutions that enable proactive, community-deliverable, or at-home interventions.

Proposed solutions may address one of two technical areas:

- Detect early-stage tooth decay and oral microbiome dysbiosis using low-cost, accessible, and quantitative diagnostic approaches prior to the need for clinical intervention
- Repair enamel through bio-inspired materials that functionally restore tooth structure, integrate with native tissue, and demonstrate superior durability to current fillings.

Concepts must define strategies to demonstrate feasibility and rigor, and should include quantitative metrics for performance (e.g., microbiome composition shifts, material durability, and biocompatibility) in appropriate early-stage model systems (biofilms, cell culture models, organoids/organ-on-chip models, etc.) to enable *in vivo* validation.

Topic 10: Ending Preventable Deaths from Ectopic Pregnancy Through First-Visit Diagnosis

Early pregnancy care urgently needs objective, point-of-care tools that allow clinicians to determine pregnancy viability and location during the first medical visit. Today, ectopic pregnancy remains difficult to diagnose, often requiring serial labs, repeat imaging, emergency visits, or referral to clinicians with advanced ultrasound expertise. Ectopic pregnancies cannot result in a viable birth and missed or delayed diagnosis can lead to rupture, hemorrhage, infertility, and preventable maternal death. Due to the emergent nature of this condition, a missed diagnosis can have disproportionate impact in rural and settings with limited access to timely advanced care.

ARPA-H seeks revolutionary technologies that can effectively resolve the diagnostic uncertainty of pregnancies of unknown location by enabling same-day differentiation of viable intrauterine pregnancy, early pregnancy loss, and ectopic pregnancy.

Proposers are encouraged to focus on one of the following areas and propose both technology development and clinical adoption approaches:

- Point-of-care tools to distinguish viable intrauterine pregnancy, failing intrauterine pregnancy, and ectopic pregnancy.
- Biomarker or multi-analyte tests to assess early pregnancy viability.
- Targeted ultrasound contrast or imaging approaches to localize nonviable pregnancies.
- Ectopic pregnancy classification and risk models to predict hemorrhage or placenta accreta spectrum.

Technologies should demonstrate improved performance over current standard of care for identifying early pregnancy location and support same-day treatment planning. Solutions must be highly innovative, clinically relevant, scientifically plausible, and designed for real-world adoption, including coverage by insurance and Medicaid. Proposers should articulate a credible pathway to clinical integration, cost reduction, and use in settings where subspecialty imaging

expertise is limited. ARPA-H seeks bold, first-of-kind approaches rather than incremental improvements to existing workflows. Additionally, ARPA-H encourages submissions of collaborations between MDs and PhDs.

Topic 11: Transforming the Well-Woman Exam through Objective Data

The well-woman exam is a trusted institution, but there is almost no objective reproductive health data to guide the interaction between the provider and the patient. In routine care, clinicians often rely on history, physical exam, and patient-reported symptoms to detect high-burden reproductive conditions such as endometriosis, Polyendocrine Metabolic Ovarian Syndrome (PMOS), fibroids, infertility, and menopause timing. As a result, many patients experience delayed diagnosis, delayed intervention, or are left to seek answers through direct-to-consumer products, particularly in areas with limited OB/GYN provider access.

While tests to detect specific diseases are emerging, they will likely be accompanied by prior authorization requirements and questions around who should be tested. An overall test of reproductive health would help determine who is referred for specialists and tested for specific reproductive disorders.

ARPA-H seeks proposals to address the lack of objective reproductive health data in routine care, which limits the value of the well-woman exam and constrains early detection of high-burden conditions. This may include novel objective screening technologies that can be used at home, in primary care, or in routine gynecologic care to identify patients who need additional evaluation for an underlying reproductive condition. This should not be focused on one specific disease, but overall reproductive health.

Proposers are encouraged to focus on solutions meeting the following guidelines:

- Screening for women with reproductive conditions such as endometriosis, PMOS, fibroids, diminished ovarian reserve, primary ovarian insufficiency, and perimenopause/menopause onset.
- Tests should aim to identify patients who warrant further evaluation by a specialist, not to provide a definitive diagnosis.
- Solutions may include point of care diagnostics, physiologic monitoring, imaging, and other reproductive organ health assessment tools.
- AI and computational techniques may be part of the solution, but solutions proposing such models as a standalone solution are discouraged.
- Technologies should focus on actionable screening and risk stratification rather than incremental improvements to exam-room devices.

Solutions should demonstrate clinically meaningful sensitivity against current standards of care, without requiring specialist referral as the first step. Successful technologies will enable earlier, more accurate detection of reproductive disorders and reproductive lifespan transitions such as perimenopause/menopause, expand the scope of the well-woman exam, and create scalable platforms that modernize women's health care. Proposed approaches must be scientifically plausible, clinically actionable, highly innovative, and designed for coverage by insurance,

including Medicaid. Additionally, ARPA-H encourages submissions of collaborations between MDs and PhDs.

Ideally, this solution will allow most women to be cared for by a family medicine provider, only being referred to an OBGYN when needed.

Topic 12: Innovations in Biotransport to Support Long-Term Preservation of Tissues and Organs

While cryopreservation advances are enabling long-term cryopreservation of increasingly larger biological form factors, preservation of whole transplantable organs is still extremely hard due to multiple technical hurdles, including cryoprotective agent (CPA) toxicity and difficulty delivering CPAs uniformly throughout tissues. For example, to prevent the formation of ice throughout the entire organ, CPAs must reach all regions at effective concentrations. Fundamental biotransport limitations, particularly restricted and nonuniform penetration of protective agents into thick, heterogeneous tissues, remain a critical barrier to achieving intracellular delivery of protective molecules at scale. These limitations prevent robust, long-term preservation and biobanking of tissues and organs at any temperature, constraining the availability, logistics, and equitable delivery of these advanced regenerative therapies. Success on this front would dramatically expand tissue and organ supply, transform transplant logistics, and broaden equitable access to tissue and organ based therapies by making long-term preservation of transplantable organs a near-term possibility.

ARPA-H seeks bold, cross-disciplinary solutions to overcome the fundamental transport limitations that currently prevent reliable preservation of thick tissues and whole organs. We are particularly interested in approaches that enable highly efficient, low-toxicity distribution and removal of protective agents throughout complex microvascular networks. Concepts that rethink organ geometry, leverage advanced materials or nanotechnology, or integrate predictive modeling with real-time feedback and automation are especially encouraged.

Proposed concepts may encompass innovations in techniques, platforms, and/or integrated technologies that:

- Achieve rapid, uniform distribution and intracellular uptake of protective molecules throughout engineered or donated tissues and intact organs with diverse geometries, dimensions, and vascular architectures;
- Quantitatively characterize and control transport using measurable, system-level parameters (e.g., effective permeability, penetration depth, saturation kinetics, spatial uniformity indices); and

Establish design rules and tunable parameters that can be tailored to specific tissue and organ types (e.g., heart, kidney, liver, composite tissues).

Concepts should be supported by clear experimental or computational strategies to demonstrate feasibility and rigor, such as:

- Model systems spanning relevant length scales (e.g., mm-scale tissue slabs to whole organs),
- Quantitative imaging or biosensing to map intratissue distribution and intracellular localization,
- Predictive modeling of transport

Robust metrics for technical performance (e.g., post-treatment viability, function, mechanical integrity, and biomarker profiles), impact, operability, and commercialization potential are expected.

Topic 13: Organs-in-Action: Next-Generation Human Tissue Platforms for Longevity, Disease, and Therapy Discovery

Nonclinical research has rapidly embraced New Approach Methodologies (NAMs), including organoids, organ-on-chip platforms, and advanced *in silico* tools, to improve human translation and reduce reliance on animal models. While these innovations represent important progress, ARPA-H is interested in tackling an even greater challenge: creating transformative, human tissue-based disease models that operate at true tissue and organ scales. ARPA-H seeks next generation human platforms that leap beyond organoids and lab-on-chips in order to capture multicellular tissue-level organization, patient-relevant complexity (e.g., immune, stromal, neural, vascular components) and dynamic biochemical processes specifically for studying longevity *in vivo*, which may include modeling capabilities for aging, disease progression, and treatment response at organ and system scales. The overarching goal is to reshape how we discover, test, and personalize interventions for longevity and across a wide range of diseases by closing the gap between traditional preclinical systems and actual human pathophysiology. Approaches must include technical, impact, operational and commercialization metrics.

Examples of potential concepts include:

- **Longitudinal “time lapse” models** that utilize human tissues (e.g., ovaries, uterus, heart, kidney, bone marrow) and are equipped with controllable “aging drivers” that accelerate key aging processes *in vitro*.
- **Multi-organ human metabolic disease circuit** by interconnecting a set of human tissue modules, such as liver, pancreas, adipose tissue, skeletal muscle, and gut epithelium with a shared microfluidic circulation to model systemic changes and recapitulate key hallmarks of metabolic disease.
- **Next-generation human lung injury and infection platform** using human lung alveolar-capillary model that includes key epithelial, endothelial, stromal, immune, and surfactant components under realistic breathing or ventilation conditions.
- **Vascularized, innervated human musculoskeletal unit for chronic pain and degeneration** by combining muscle, tendon, bone, and cartilage with integrated blood vessels and sensory/motor neurons to engineer a system that can be subjected to controlled mechanical loading and inflammatory or injury signals, with readouts of electrophysiology, contractile function, and pain signaling.

ARPA-H is particularly interested in platforms that:

- Directly connect with new approach clinical trials using NAMs with high potential for regulatory clearance;
- Integrate emerging organ-scale or high-throughput organoid/organ-on-chip technologies, native and/or engineered tissues, synthetic biology, and rich *in situ* data streams;
- Support high-throughput perturbation and longitudinal molecular, functional, and structural measurements; and
- Undergo rigorous validation against human clinical and real-world data

Topic 14: Near real-time, Non-contact Determination of Sterility in Distributed Manufacturing Systems

Distributed manufacturing systems shrink manufacturing footprints from large warehouse sized buildings making tens of thousands of units at once, to small often portable systems making tens of units at once. One of the major use cases for distributed manufacturing is to shorten supply chains, bringing products closer to the users, and creating an on-demand production capacity. However, many of the quality control steps used at large manufacturing sites for huge volumes of product do not translate directly into small automated systems that are producing small batches. Most distributed systems require miniaturized, automated, and real time sensors to fulfill the quality assurance and testing functions that a team of quality engineers and systems would normally perform. Sterility assessments are typically reliant on colony growth metrics applied to filter membranes or directly through inoculation. Other methods that determine bio-burden still typically require direct access to the substance being tested and often cannot measure a sterility assurance level (SAL) of 10^{-6} .

ARPA-H seeks truly innovative, cross-disciplinary solutions that can overcome the time limitations of current tests which take between three (3) and 14 days, as well as batch size limitations. When a batch is less than 10 units, destructively testing a unit for sterility is functionally impractical. Detection of organic molecules is not sufficient for sterility determinations due to the need to test for the viability of any microorganisms. ARPA-H is particularly interested in non-contact evaluation technologies that can measure the presence and amount of metabolic activity within a clear container filled with sterile solutions of small molecule or biologic prescription drugs. Concepts that rethink the measurement of biologic activity, leverage novel spectroscopy techniques, advanced or active materials, and integrate predictive modeling techniques are especially encouraged.

Proposed concepts may use any technology platform or technique that:

- Rapidly evaluate variable volumes (2milliliters – 1 liter) of sterile pharmaceuticals in their original containers without compromising the sterility of the sample
- Quantitatively measure metabolic activity in samples down to a SAL of 10^{-6}
- Create sampling models for common sample form factors
- Reduce the space and time required to perform sterility testing so that it could be feasibly done in-line with distributed manufacturing systems

Concepts should be supported by clear experimental and computational strategies demonstrating feasibility, including:

- Flexible parameter space that can be tailored to specific categories of molecules and drugs.
- Verification testing for major modes of interference and cross-reactivity in multiple use cases
- Validation processes for predictive models of metabolic activity

Robust metrics for technical performance (e.g., speed, minimum level of detection), operability, viable scenarios for use, overall impact, and commercialization potential are expected.

Topic 15: ICAT (In-Cavity Adjuvant Therapy): Implantable Systems for Local Cancer Control at the Resection Margin

Surgery is oncology's most common intervention, with over 80% of the ~15 million¹ new cancer cases each year requiring an operation, roughly 12 million surgeries globally. Yet the mean positive surgical margin rate is 8.8%, reaching 21% to 35% in some tumor types,² because local anatomy often forbids adequately wide margins (e.g., brain, head and neck, pancreatic head) or residual disease is simply missed. Residual disease must then be treated with subsequent high-morbidity therapies such as systemic chemotherapy or radiation. ARPA-H seeks to enable adjuvant therapy delivered locally into the resection cavity beginning at the time of surgery, treating the margins the surgeon cannot remove, ideally replacing systemic adjuvant therapy or radiation with continuous, adjustable local control. The vision is a closed-loop implant in which local drug delivery is governed by in-situ sensor measurements of residual or recurrent disease, dosing where and when it is needed. This would transform local recurrence from a systemically managed blind spot into a directly treatable target, sparing patients systemic toxicity and, in some cases, enabling function-preserving rather than radical surgery. Materials, sensing, and closed-loop delivery sit in separate silos, and a solution that combines them is an ARPA-hard problem no single funder or company will take on. The topic spans two (2) technical areas, sensor-based detection of residual disease and localized therapeutic delivery. Given the funding scope of this effort, proposals addressing either area alone are permissible.

Treatment: A cavity-conforming, radiotranslucent, biocompatible implant that delivers therapy into the peri-cavity rim with a steep, tunable dose gradient, high at the margin and low in adjacent healthy tissue. Delivery medium and therapeutic payload are open to innovation, with sustained, controllable release preferred over a single bolus. The aim is to decouple local dose from systemic toxicity and reach the infiltrating cells responsible for recurrence, a combination no current approach achieves.

Sensing: Continuous in-situ detection of residual or recurrent disease capable of being coupled to on-demand release, enabling closed-loop local dosing. Sensing that is designed to interface with delivery is preferred, though sensing capability alone is responsive.

Examples of potential concepts include:

- Closed-loop sense-and-respond implant in which in-situ detection of residual or recurrent disease triggers localized dosing, demonstrated in a glioblastoma model

(the clearest case of biologically local failure) and architected to generalize to other constrained-margin sites.

- Localized delivery system that distributes therapy across the full infiltrated margin with a steep, tunable, spatially controllable dose gradient, high at the margin and low in adjacent healthy or eloquent tissue.
- Implantable residual-disease sensor providing continuous in-situ measurement of margin status or early recurrence, with an output suitable for triggering on-demand local therapy.

ARPA-H is particularly interested in platforms that:

- Achieve a steep controllable dose gradient that reaches the full zone of residual disease while sparing adjacent healthy tissue.
- Integrate emerging tissue-matched materials, conformal bioelectronics, controlled-release chemistries, and in-situ sensing into a single implantable system.
- Maintain conformal contact and function across a moving, healing resection cavity.
- Are positioned within a multimodal treatment strategy and could advance along a combination-product (device plus drug) regulatory pathway.

Topic 16: Causally-Grounded Alignment for Clinical Generative Artificial Intelligence Tools

Generative AI is being rapidly adopted for clinical decision-making, yet today's systems learn predominantly from statistical association rather than cause and effect and do not necessarily align with patients' goals. A clinical model may "learn" that an intervention is beneficial because it co-occurs with recovery in the training data, not because it drives recovery, a failure mode that remains invisible under standard accuracy benchmarks but produces harmful or unaligned recommendations when a model encounters patients unlike those it was trained on. Current alignment methods (e.g., reinforcement learning from human feedback, guardrail prompting, and red-teaming, etc.) approach clinical AI as a text-in/text-out system and treat misalignment primarily as a data-bias issue. However, this overlooks the deeper challenge: models often exploit confounded correlations, failing to address the need for causal reasoning and true alignment with clinical values. On the other hand, a model over-aligned with patient expectations may also be harmful as it may not push back against potential dangerous or inappropriate expectations, e.g. antibiotics for viral infections.

ARPA-H seeks approaches that align clinical foundation models to clinical reasoning and patient values and then confirms that alignment through independent mechanistic auditing and validation. By grounding both alignment and verification in identifiable causal pathways, this effort aims to make clinical AI trustworthy and patient-centric under real-world distribution shift.

Examples of potential concepts include:

- **Causal alignment constraints** that are grounded in counterfactual and identifiability requirements, coupled with an evaluator that quantifies insufficient causal grounding and mitigates cascading errors.

- **Multi vector alignment** is essential for AI tools that can produce broadly acceptable outputs that balance values and preferences from multiple different actors (e.g., patients, clinicians, caregivers, etc).
- **Clinical focus** should be on populations and disease states where patient values as opposed to algorithmic guidelines are a major determinant of clinical decision making e.g., elder care.

ARPA-H is particularly interested in approaches that:

- Employ alignment methods that generalize across sites, populations, and time, validated against clinician gold-standard reasoning
- Establish a shared causal foundation linking alignment and verification, laying the groundwork for credible, generalizable clinical AI and mechanism-grounded verification;
- Enable clinical AI that provides outputs that can adapt to dynamic clinical conditions and values to provide outputs that are more acceptable to patients and clinicians than generic AI tools.

2.4 PROPOSERS

An organization / proposer may have multiple submissions; however, each submission must have a different Project Lead. Project Leads can only submit to one (1) topic area and cannot submit more than (1) solution summary, and one (1) full proposal. **Project Leads must meet EHI eligibility criteria as per section 2.6.** See Section 1.2 for Project Lead definition. The Government's expectation is that all key members of the performer team will be onboard within 60 days of the award. If an organization / proposer has multiple submissions with the **same Project Lead**, all submissions after the first submission received will be determined to be non-conforming.

The full proposal submissions must demonstrate the expertise needed to collectively achieve the goals of the proposed topic. Communications, networking, and team formation are the sole responsibility of the proposer. Proposals must be led by one (1) early-career investigator, as defined in Section 1.2. Proposers must submit a Task Description Document (TDD) describing the work they will accomplish either independently with their organizational team or in collaboration with subawardees and consultants. Subawardee and consultant costs cannot exceed 30% of the total value of the OT Agreement.

2.5 TENTATIVE EHI PROGRAM MEETINGS AND ATTENDANCE

This information is provided for time and resource planning purposes.

- **Annual In-Person Meeting** - The budget must include travel and attendance costs for an on-site EHI annual meeting for the project lead and one additional attendee. All EHI performers will present updates on their projects to ARPA-H, other Government agencies and invited guests. ARPA-H anticipates that each event will require four (4) days (two (2) days for the event, and two (2) days for travel).

- **Networking Events and Workshops** – Proposed costs must include travel and attendance for one (1) on-site EHI networking event or workshop per year, for the project lead and one (1) additional attendee. In addition to this required event, performers are encouraged – but not required – to attend other networking events and workshops with the broader Health and Human Services (HHS) community, other agencies, and potential partners. ARPA-H anticipates that the required EHI event will require four (4) days (2 days for the event, and 2 days for travel).
- **Monthly Status Reports (MSR) with Program Manager (PM)/EHI Team** – Each project lead will be required to meet virtually for one (1) hour with the PM/EHI team at least monthly to review progress, metrics, milestones, and deliverables, as determined in the final award. Status reports outlining technical and financial updates will be required at monthly meetings with the PM.

2.6 ELIGIBILITY INFORMATION

All responsible sources capable of satisfying the Government's needs and meeting the eligibility criteria listed below may submit a solution summary and proposal to this ISO.

While there is statutory language that suggest ARPA-H is limited in the number of awards it may make to one (1) entity, ARPA-H reserves the right to award to more than one Project Lead affiliated with the same organization, or to the same organization across different funding cycles, provided each award results from a separate, conforming proposal submitted in compliance with Section 2.4's one-proposal-per-entity limit for this ISO. ARPA-H encourages organizations to submit their research ideas notwithstanding this perceived limitation. Selection for award remains at the sole discretion of ARPA-H and is not guaranteed, regardless of the Government's interest in a given proposal.

Eligibility

Proposal submissions must be led by an early-career principal investigators (academic, non-profit, industry etc.) who is within 8 years after completion of their first terminal degree (leaves of absence, post-doctoral, residency, and fellowship periods can be excluded for determination of eligibility). The EHI program initiative welcomes potential proposers that meet the following eligibility criteria:

- All proposers and proposed team members must be employed at a U.S. institution, which includes those in U.S. states and territories.
- Proposers who have participated as a prime (project lead) on an award from any ARPA agency (e.g., DARPA, IARPA, ARPA-E, etc.) are not eligible to apply to EHI.
- The proposer's concept has not already received funding or been selected for award negotiation under another funding opportunity, whether from ARPA-H or another Government agency.
- Post-doctoral fellows/trainees and clinical trainees cannot be project leads, but it is highly encouraged to include them as support staff.

- Federally Funded Research and Development Centers, University Affiliated Research Centers, National Laboratories, or other Government entities are not eligible to receive funding under this initiative.
- Non-U.S. individuals employed by U.S. institutions may participate to the extent that such participants comply with any necessary nondisclosure agreements, security regulations, export control laws, and other governing statutes as applicable

NOTE: Proposal submissions from non-eligible proposers will be deemed non-conforming and will be rejected without further review.

Non-U.S. Entities

Proposals from non-U.S. entities **will not be accepted**. All proposers and proposed team members **must** be employed at a U.S. institution, which includes those in U.S. states and territories.

2.7 SYSTEM FOR AWARD MANAGEMENT (SAM)

All proposer organizations must have an active registration in SAM.gov at the time of proposal submission for their proposal to be determined conforming. Proposers must maintain an active registration in SAM.gov with current information at all times during proposal consideration and during the performance period of an active ARPA-H award. Registration is available at [SAM.gov](https://sam.gov).

NOTE: New registrations, as well as renewals, may take more than 14 business days to process in SAM.gov and is independent of ARPA-H. As such, ARPA-H representatives have no influence over processing timeframes.

3. EHI SUBMISSION AND EVALUATION PROCESS

3.1 SUBMISSION PROCESS OVERVIEW

The EHI Initiative uses a two-step submission process, described below.

Step 1: Solution Summary Submission. Proposers submit a Solution Summary, a two (2)-page document providing an overview of the proposed solution and its impact on the field. Proposers must submit a Solution Summary to be eligible to submit a Full Proposal at Step 2.

After reviewing the Solution Summary, ARPA-H will notify the proposer only of a determination to either "encourage" or "discourage" submission of a Full Proposal. No additional feedback, written or verbal, will be provided at this stage. All proposers who submit a conforming Solution Summary, whether encouraged or discouraged, remain eligible to submit a Full Proposal at Step 2.

Step 2: Full Proposal Submission. Proposers must prepare and submit a full proposal in accordance with the instructions and templates provided in Attachments B, C, D, E, and F. The full proposal format enables proposers to expand upon and fully articulate their concept for ARPA-H's evaluation.

Proposers selected to negotiate an award following Step 2 may be asked to submit additional documentation to support negotiation of an OT Agreement.

Additional requirements specific to each step are provided in Sections 3.2 and 3.3.

Conforming submissions contain all requirements detailed in this ISO and required attachments. Solution summaries and full proposals that fail to include required information may be deemed non-conforming and may be removed from further consideration. A solution summary or full proposal can be deemed non-conforming under this ISO if it fails to meet one or more of the following solicitation requirements:

- The proposed solution is applicable to the EHI program TAs.
- The proposers meet the eligibility requirements.
- The solution summary/full proposal meets the submission requirements.
- The solution summary/full proposal meets the content and formatting requirements in the attached instructions.
- The proposer's concept has not already received funding or been selected for award negotiations for another funding opportunity (whether from ARPA-H or another Government agency).
- Non-conforming solution summary and full proposal submissions may be removed from consideration. Proposers will be notified of non-conforming determinations via email correspondence.

3.2 SOLUTION SUMMARY SUBMISSIONS

Solution Summaries shall not exceed a maximum of two (2) pages, excluding the cover page. See Attachment A for additional guidance on preparing the Solution Summary.

Solution Summaries and full proposals will be assigned to an ARPA-H Program Manager (PM) with interests and expertise closely related to the proposer's research TA. The PM will act as project manager and mentor to EHI award recipients.

Solution Summaries will undergo a "blind" review and must be completely anonymized upon submission. Proposers must not include any identifying information about the PI, organization, or team members within the body of the Solution Summary template (items 1 through 3), as described in the Attachment A instructions. All identifying information must be included on the coversheet pages only. Failure to anonymize the Solution Summary may result in the submission being determined non-conforming.

3.3 FULL PROPOSAL SUBMISSIONS

ARPA-H recognizes that preparing a full proposal requires considerably more effort than preparing a Solution Summary. See Attachments B, C, D, E, and F for additional guidance on preparing the Full Proposal. A "discourage" notification at Step 1 is intended to save proposers the time, effort, and expense of preparing a Full Proposal when selection for award is highly unlikely.

3.4 SUBMISSION INFORMATION

All Solution Summaries and full proposals submitted in response to this solicitation must be written and presented in English and must be consistent with the content and formatting requirements provided in the corresponding attachments.

Proposers are responsible for submitting their Solution Summary and full proposal via the [ARPA-H Solutions site \(https://solutions.arpa-h.gov/home\)](https://solutions.arpa-h.gov/home) and ensuring receipt by the date and time specified in this ISO or as communicated through feedback letters. No other method of submission is permitted.

Registration is required to submit via the ARPA-H Solutions site.

NOTE: Non-conforming submissions that do not follow ISO instructions will be rejected without further review at any stage of the process.

3.5 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."

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.

3.6 REVIEW, EVALUATION, AND SELECTION PROCESS FOR AWARD

It is ARPA-H policy to ensure impartial and comprehensive evaluations of each conforming full proposal, based solely on the evaluation criteria listed below. Selection for award negotiation will be made to proposers with solutions determined to be most advantageous to the Government.

NOTE: Full proposals will not be evaluated against each other but rather evaluated on their own individual merit to determine how well the submission meets the criteria stated in this ISO.

Review and Evaluation Timelines

ARPA-H intends to review solution summaries and full proposals as soon as possible after the closing of the submission deadlines.

Evaluation Criteria for Step 1 - Solution Summaries

Solution Summaries will be evaluated based on the proposed solution's alignment with the selected TA, its technical merit and innovativeness, and its potential relevance and contribution to the ARPA-H mission. This review will result in a determination to encourage or discourage submission of a full proposal.

Evaluation Criteria for Step 2 - Full Proposal and Award

Full proposals will be evaluated using the following criteria listed in descending order of importance.

Criteria 1: Overall Scientific and Technical Merit

The proposed technical approach is innovative, feasible, achievable, 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 clearly defines feasible planned mitigation efforts. In addition, the evaluation may take into consideration the extent to which the proposed IP rights structure and software components will potentially impact the ability to commercialize the technology and adhere to open-source solutions and/or standards.

Criteria 2: Potential Contribution and Relevance to the ARPA-H Mission

The potential contributions of the proposed effort support ARPA-H's mission to accelerate better health outcomes for all will be evaluated. The proposed efforts demonstrate potential to invigorate exceptionally innovative and impactful health and biomedical research more broadly in the nation should be evident. The proposed intellectual property restrictions (if any) will not significantly impact the Government's ability to transition the technology.

Criteria 3: Assessment of Proposed Cost/Price

ARPA-H will evaluate whether the proposed price is reasonable for the proposed technical approach, TDD, milestones, and expected outcomes. The Government may use price analysis, comparison to other similar proposed prices or efforts, value analysis, and/or request additional supporting information as needed to substantiate the proposed price.

Handling of Competition Sensitive Information

ARPA-H policy is to protect all solution summaries, proposals and related submission materials as competition sensitive information and to disclose their contents only for the purpose of evaluation and/or 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. ARPA-H may solicit input on technical aspects of the solution summaries and proposals from non-Government consultants/experts who are strictly bound by appropriate non-disclosure requirements. No submissions will be returned.

3.7 EVALUATION AND AWARD DISCLAIMERS

The Government reserves the right to select for negotiation all, some, one, or none of the proposals received in response to this ISO. Consistent with the award structure described in

Section 2.2, the Government reserves the right to fund only the 24-month base period of a proposal, or to fund the base period together with the 12-month Director's Award option period, at the Government's sole discretion. Negotiations will commence upon selection notification.

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, conditions, price, and/or if the proposer fails to provide requested additional information in a timely manner.

In all cases, the Government will have sole discretion to negotiate all instrument terms and conditions with selectees. ARPA-H will apply publication or other restrictions, as necessary, if it is determined 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, any information marked Sensitive but Unclassified (SBU), etc. Any award resulting from such a determination will include a requirement for ARPA-H concurrence before publishing any information or results on the effort. At a minimum, all awards will include a requirement for performer teams to submit information for review to ARPA-H before publishing.

4. POLICY REQUIREMENTS AND MISCELLANEOUS OTHER INFORMATION

4.1 CONTROLLED UNCLASSIFIED INFORMATION (cui) ON NON-FEDERAL INFORMATION SYSTEMS

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

4.2 ORGANIZATIONAL CONFLICTS OF INTEREST (OCI)

The proposer, through submission of a proposal, is required to identify and disclose all facts relevant to any potential OCI involving the proposer, its organization, and/or any proposed team member (i.e. proposed subawardee). Along with the disclosure, the proposer may be required to submit a mitigation plan, which is a description of the action the proposer has taken to avoid, neutralize, or mitigate the stated OCI. The Government may require the proposer to provide additional information to assist the Government in evaluating the OCI mitigation plan. The disclosure and mitigation plan(s) do not count toward the page limit.

If the Government determines the proposer failed to fully disclose an OCI; or failed to provide the affirmation of ARPA-H support; 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.

4.3 AGENCY SUPPLEMENTAL OCI POLICY

ARPA-H restricts performers from concurrently providing professional support services, or similar support services and being a technical performer. Therefore, as part of the organizational conflict of interest disclosure requirement above, a proposer must affirm whether the proposer or any proposed team member (proposed subawardee, etc.) 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 (1) calendar year prior to the proposal's submission date.

Proposers shall follow the instructions in and complete the required templates to address the requirements of this ISO Section.

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

4.4 RESEARCH SECURITY DISCLOSURES

In accordance with [NSPM-33](#), research organizations should identify and mitigate conflicts of commitment (COCs) and conflicts of interest (COIs) to receive federal funding. A research organization proposing to this ISO will be required to provide additional documentation as requested for Key Personnel for ARPA-H to determine the existence of any risk. The format for this submission can be found in the Administrative and National Policy Requirements Document (Attachment F).

4.5 INTELLECTUAL PROPERTY (IP)

Proposers shall provide a good faith representation that the proposer either owns or possesses the appropriate licensing rights to all 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 (including source code), 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.

4.6 HUMAN SUBJECTS RESEARCH

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.

4.7 ANIMAL SUBJECTS RESEARCH

All entities submitting a proposal for funding that will involve engagement in animal subjects research (award recipients performing research, experimentation, or testing involving the use of animals) must 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 provide documentation of a current Animal Welfare Assurance (AWA) on file with the Office of Laboratory Animal Welfare (OLAW).

Proposers must complete and submit the Vertebrate Animal Section (VAS) for all proposed research anticipating animal subjects research. A guide for completing the VAS can be found at <https://olaw.nih.gov/sites/default/files/VASchecklist.pdf> worksheet for all proposed research anticipating Animal Subject Research.

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.

4.8 ELECTRONIC INVOICING AND PAYMENTS

Performers will be required to submit invoices in a designated electronic payment system, as described in the award document.

4.9 GOVERNMENT-FURNISHED PROPERTY/EQUIPMENT/INFORMATION

Government-furnished property (GFP)/equipment (GFE)/information (GFI) may be provided to selected performers. Any instances of GFP/GFE/GFI will be specifically negotiated.