INNOVATIVE SOLUTIONS OPENING

FOR

BIOMOLECULAR GRAMMAR FOR PROTEIN AGGREGATION MODULATION AND INTERVENTION

BIOGAMI

HEALTH SCIENCE FUTURES

ARPA-H-SOL-26-149

January 30, 2026

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INNOVATIVE SOLUTIONS OPENING (ISO) SUMMARY INFORMATION

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

PROGRAM TITLE: BIOmolecular Grammar for protein Aggregation Modulation and Intervention (BIOGAMI)

ANNOUNCEMENT TYPE: Innovative Solutions Opening (ISO)

ISO SOLICITATION NUMBER: ARPA-H-SOL-26-149

ISO CONTACT: BIOGAMI@arpa-h.gov

ANTICIPATED AWARDS: Multiple Other Transaction (OT) Agreements

DATES: (All times listed are Eastern Time)

Proposers' Day: Friday, February 20, 2026
Solution Summaries due date (Closing Date): Wednesday, March 4, 2026, 12 PM ET
Questions & Answers (Q&A) due date: Wednesday, March 11, 12 PM ET
Full Proposals due date: Wednesday, April 15, 2026, 12 PM ET

WHERE TO SUBMIT:

Solution Summaries: https://solutions.arpa-h.gov/Submit-Solution/
Proposals: https://solutions.arpa-h.gov/Submit-Proposal/
Questions: https://solutions.arpa-h.gov/Ask-A-Question/

PROPOSERS' DAY

ARPA-H will host a Proposers' Day in support of the BIOGAMI Program as described in Special Notice ARPA-H-SN-26-149. The purpose is to provide potential proposers with information on the BIOGAMI program, promote additional discussions, and encourage teaming and networking.

Interested proposers are not required to attend, and materials formally presented during Proposers' Day will be posted to the ARPA-H Program Website.

ARPA-H will not reimburse potential proposers for participation at Proposers' Day (or time and effort related to submissions in response to this ISO).

1. THE PROGRAM

1.1 BIOGAMI OVERVIEW

The BIOmolecular Grammar for protein Aggregation Modulation and Intervention (BIOGAMI) program aims to fundamentally transform therapeutic approaches to protein dysfunction in disease by controlling protein folding rather than treating symptoms of malfunctioning proteins. Common to neurodegenerative diseases (NDD) (i.e., Alzheimer's disease, Huntington's disease, Amyotrophic Lateral Sclerosis, and Parkinson's disease), cancers, and diabetes, are intrinsically disordered proteins (IDPs) that misfold or aggregate. Through novel AI-driven prediction tools, BIOGAMI will develop new classes of therapeutics that prevent misfolding and aggregation before they start, thus preventing many of these diseases.

BIOGAMI will bring about a transformational frameshift in how we target NDDs from trying to treat the aggregates after they've already formed and have caused damage, to tackling the problem upstream and preventing aggregation in the first place. BIOGAMI will address the root cause of chronic and degenerative illness by designing novel therapeutic modalities that (1) interfere with or prevent IDP misfolding and aggregation while preserving critical functions; and/or (2) disrupt existing oligomers and aggregates. BIOGAMI will also develop novel sensors and/or biomarkers that indicate early-stage IDP aggregation.

The classical view of protein folding holds that, after a protein has been produced as a linear string of amino acids, the unfolded protein rapidly takes on a three-dimensional structure that enables its function(s). However, approximately 70% of the human proteome contains intrinsically disordered regions (IDRs). Unlike folded protein domains that are defined by a small number of structures reliably predicted from their sequence, IDRs exist in a dynamic state with rapid evolution through a series of possible conformations. IDR sequences can expand, contract, and adopt new structures in response to changes in temperature, phosphorylation, methylation, salt concentration, pH, molecular crowding, etc. IDRs provide proteins with the flexibility critical for complex cellular processes and drive the formation of biomolecular condensates and membraneless organelles. IDR-driven biomolecular condensate formation enables high concentrations of proteins to carry out diverse critical roles in healthy cellular function. The unifying feature of these processes is that they are dynamic and transient in nature – often driven by the flexible interactions of IDR domains themselves and by interactions with other macromolecules such as nucleic acids. However, this flexibility also increases the likelihood of protein dysfunction and pathological aggregation, and indeed it does for many IDR-containing proteins implicated in human disease (e.g., amyloid beta, alpha-synuclein, TDP43, p53, etc.).

While recent advances in computational models have improved the ability to predict protein structure and function based on amino acid composition, IDRs have been

insufficiently mapped. Large gaps remain in our understanding of how heterogeneity in conformational states leads to disease, prohibiting our ability to adequately target disease proteins. Traditional approaches to uncovering protein structure, including X-ray crystallography, are prohibited by the intrinsically disordered nature of aggregation-prone proteins. Moreover, the context-dependence, heterogeneity, and dynamic nature of IDR domains are difficult to capture by nuclear magnetic resonance spectroscopy (NMR). Small angle x-ray scattering (SAXS), single molecule fluorescence spectroscopy (smFRET) and cryogenic electron microscopy (cryoEM) provide routes to identify conformational states, but require access to expensive, specialized facilities and SAXS necessitates very high concentrations of protein. Post-translational modifications and protein-protein interactions have critical impacts on IDR conformational states that add to the complexity of uncovering key disease contexts.

Protein misfolding and aggregation underlie a broad array of human diseases, including neurodegenerative diseases (NDDs), rare but lethal prion diseases, several of the most prevalent, costly and high mortality chronic illnesses (e.g., cancer, Type II diabetes and heart disease), latent viral infections, and traumatic brain injury. Unfortunately, up to 80% of proteins involved in disease are considered "undruggable" and are often only detectable once severe symptoms arise, and irreversible damage has been done. For many of these diseases, current treatment approaches poorly address symptoms, rather than the root cause of disease.

The goals of the BIOGAMI program are to leverage cutting edge technologies to accurately predict and control protein folding to treat root causes of disease and to enable early detection of diseased, misfolded proteins, opening the door to a new class of therapeutics for currently undruggable targets.

1.2 BACKGROUND AND MOTIVATION

The BIOGAMI program focuses on closing the key gaps that prevent the more rapid and effective development of therapeutics by targeting early stages of protein misfolding and aggregation. Foundational advancements in our understanding of the biochemical consequences of misfolded, "prion-like," and intrinsically disordered proteins have expanded the aperture on the critical roles these alternative protein conformations play in a wide variety of NDDs, as well as infectious agents (e.g., prions), common chronic diseases, and rare diseases. The appreciation of these misfolded protein states as pathological mediators of disease has created a vast opportunity space to develop platform tools and capabilities essential for the rapid discovery, optimization, and prototyping of novel candidate molecules to treat diseases driven by protein aggregation for which no effective therapeutic solutions currently exist.

BIOGAMI seeks to develop technology to:

(1) predict and modulate pathological consequences of protein misfolding and aggregation *in vivo*;

(2) identify and validate novel indicators of early protein misfolding for disease detection.

To achieve these goals, BIOGAMI aims to develop a comprehensive suite of novel *in silico*, test tube-based, cell-based, and model organism systems that recapitulate accurate protein misfolding across different diseases, ultimately allowing for facile screening, iteration, and optimization of potential therapeutic targets and candidate molecules. BIOGAMI will leverage these *in vivo* and *in vitro* systems to develop tools that can identify novel biological targets and initiate, manipulate, and – most critically - reverse protein misfolding cascades to prevent or halt disease. While NDDs and other peripheral protein misfolding disorders manifest as seemingly disparate clinical disorders, this program aims to target the overlapping mechanisms and pathways of pathological protein misfolding and dysfunction to catalyze disruptive innovation. By unlocking the "molecular rules" that govern IDR behavior we can open the door to novel therapeutics or prevention tools that control protein misfolding and aggregation.

BIOGAMI's goals are only now within reach due to a confluence of revolutionary technical capabilities coupled with advances in foundational basic sciences that have created a discovery framework that can be exploited to drive innovation in therapeutic discovery for protein misfolding and aggregation. BIOGAMI will bridge siloes between rare and chronic diseases, and between NDDs and peripheral protein misfolding disorders to both invest in areas with unmet needs as well as demonstrate technological applicability across more prevalent diseases. BIOGAMI aims to develop approaches to detect, target, and prevent the earliest stages of potential aberrant misfolding and aggregation, in contrast to current approaches that intervene at later stages of aggregation.

1.3 ENABLING TECHNOLOGIES

The enabling technologies and developments that performers may leverage for BIOGAMI include, but are not limited to, the following:

- **Advanced Biophysics and Imaging Techniques:** Including nuclear magnetic resonance (NMR), small angle X-ray scattering (SAXS), cryo-electron microscopy (cryoEM), single-molecule fluorescence resonance energy transfer (smFRET).

- **Molecular Dynamics Simulations and Other Computational Models:** Including novel applications of machine learning, rational sequence design and simulations and techniques expanding our capabilities to predict IDR conformational ensembles are within scope but must be combined with experimental studies, including across IDR sequences for how proximity to folded domains, post-translational modifications beyond phosphorylation, or protein-protein interactions (particularly within condensates) influence IDR structure.

- **High Throughput Assays of Protein Interactors and Function:** Including high throughput fluorescent assays, mutational scanning and novel applications of machine learning in cellular, plant, and small animal models to increase our understanding of the IDR sequences and features corresponding to specific known protein functions commonly associated with IDR-containing proteins.

2. BIOGAMI STRUCTURE, TIMELINE, AND TECHNICAL APPROACH

2.1 PROGRAM PHASES AND TIMELINE

The BIOGAMI program will develop a generalizable, comprehensive, and reusable computational and experimental platform for disordered proteins across multiple diseases to:

- Reliably modulate of **how** disordered proteins fold to prevent protein misfolding and aggregation before they start, while preserving the key functions of these flexible proteins
- Design and validate novel indicators of protein misfolding and intermediate states of protein aggregation for early detection

To accomplish these goals, BIOGAMI is structured into two Technical Areas (TAs) over two 24-month Phases:

Phase 1 (0-24 months) (1) Establish a foundational model of IDP dynamics, structural changes, and aggregation; and (2) demonstrate that molecules can target dynamic intermediate states to prevent 'disease' conformations and aggregation, and serve as sensors and/or biomarkers of protein aggregation.

Phase 2 (25-48 months) Translate Phase 1 work through demonstration that molecules targeting dynamic intermediate states of IDPs can be effective as preventative therapies and as early sensors of protein dysfunction.

Selection for performer teams to advance to the next phase of the BIOGAMI program will take place at the end of Phase 1 based on completion of technical metrics.

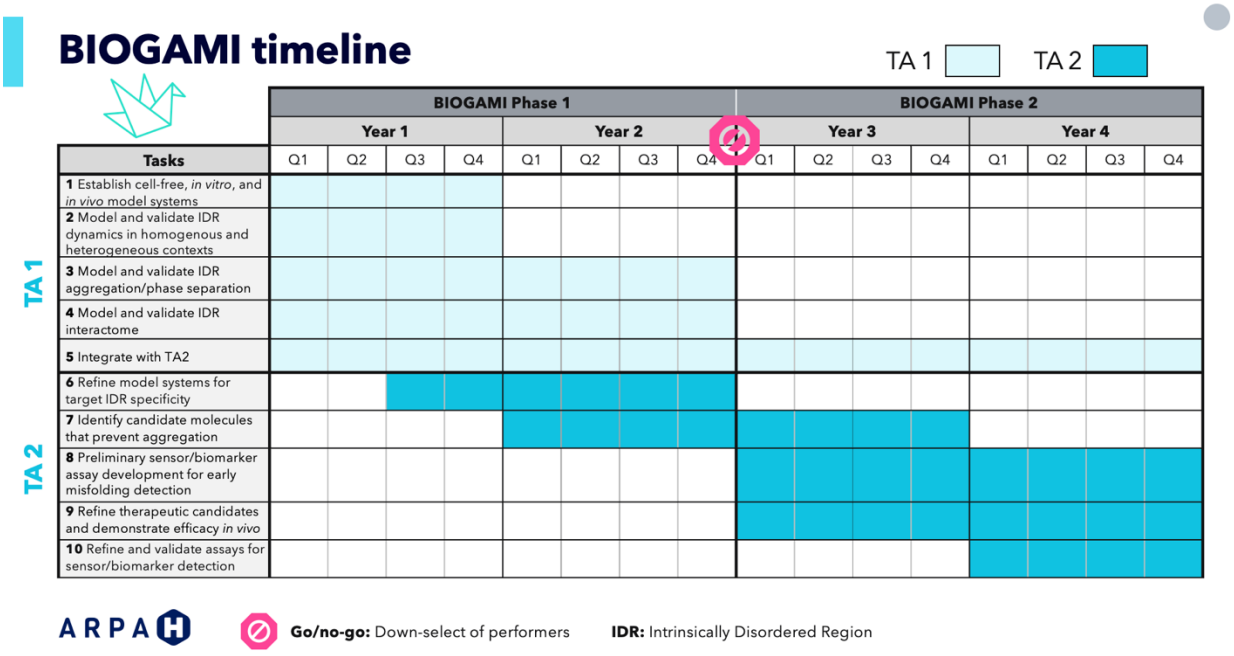

Figure 1. BIOGAMI program structure by phase and year. Note that while most of the work for TA2 will occur in Phase 2, proposers may adjust the months as needed in their task description document to encompass tasks determined to be necessary in Phase 1 to lay the groundwork for TA2.

2.2 TECHNICAL AREAS (TA)

There are two Technical Areas (TAs) for innovation, described below. Performers **must** propose a research program for **both** TAs.

TA1 – Establish the molecular grammar of IDRs

The goal of TA1 is to determine the primary sequence, secondary protein features, and environmental conditions that regulate IDR behavior in diverse proteins, culminating in a foundational model for IDR "molecular grammar." The heterogeneity and dynamic nature of IDR domains present significant challenges in protein mapping with traditional techniques, preventing innovation in the therapeutic targeting of protein misfolding, biomolecular condensate formation, and aggregation. Solutions shall integrate computational and experimental methods to characterize diverse and dynamic IDR structural ensembles and leverage novel discoveries allowing for prediction of subcellular localization of proteins, whether within membrane-bound organelles or phase-separated biomolecular condensates based on amino acid sequences that lay the foundation for defining the dynamics of biomolecular condensates. TA1 should develop test tube- and cell-based high throughput experimental screening platforms to establish and validate predictive computational models that will be foundational towards:

(1) understanding poorly defined functions of proteins with IDRs;
(2) enabling a novel drug discovery pipeline that can accurately detect aberrant IDR behavior in the disease context as well as identify drug candidates specifically targeting pathways of aberrant IDR behavior.

Proposers are expected to provide detailed information on the computational and experimental screening methods proposed to develop a foundational model of IDR domains. Proposers should clearly articulate methods for discovery and discuss strengths and mitigation plans for technical risks.

- **Computational methods:** For AI/ML algorithms, proposals should discuss parameters and details, such as training data acquisition and augmentation procedures, input data pre-processing/cleaning steps, input data quality control, characteristics of training/test data, procedures for detailing with missing data, availability of data for training, and methods for updating the algorithm after deployment.
- ***In vitro* and *in vivo* models:** Proposals must include rationale for test tube-based, cell culture-based, and animal models to characterize and validate a broad diversity of IDR structural ensembles, biomolecular condensate formation and dynamics, aggregation kinetics, etc. In particular, inclusion of high-throughput alternative animal models such as *C. elegans*, zebrafish or *Xenopus* embryos must be justified in the proposal. Key information such as assay robustness, sensitivity, dynamic range, concentrations, and alternative assay approaches and substrates should be included.
- **All approaches:** Submissions must describe model throughput, scaling, and speed, as well as the breadth and depth of sequence diversity and functional space to be sampled.
- BIOGAMI metrics require validation of TA1 foundational model predictions. Proposals must provide details of validation strategy.

The ideal BIOGAMI TA1 discovery pipeline would be able to detect, predict the structure(s) and aggregation potential of, and characterize an IDP or IDR-containing protein. By the end of Phase 2, proposers must be able to predict and validate protein properties, including IDR structure, dynamics, biomolecular condensate formation, aggregation and the types of interactions possible (interactome) as a proxy for protein function, within 60 days when challenged with an IDR sequence.

Ultimately, BIOGAMI TA1 pipelines will be leveraged in TA2 to rapidly nominate lead drug candidates as well as validate translational sensors and/or biomarkers to be able to rapidly detect and modulate IDR protein folding *in vitro* and *in vivo*.

<u>TA2 – Modulate IDPs to detect and control protein folding</u>

The goal of TA2 is to validate the foundational model created in TA1 for potential detection and therapeutic applications. Solutions shall:

(1) reverse protein aggregation and restore protein function and/or prevent aggregation in the first place;
(2) validate clinically translatable indicators or early detection of protein misfolding in human tissues and in preclinical *in vivo*/organoid models

Modulating protein aggregation may rely on a two-pronged approach both to destabilize aggregates or soluble intermediates and to ensure proper refolding and functionality of target proteins by leveraging structure-based approaches of TA1.

Solutions may leverage high resolution structures and AI modeling to enable both disease and context-specific conditions, as well as broadly shared mechanisms of protein re-folding. Molecular dynamics simulations will allow for more effective *in vitro* models that recapitulate disease features and precision targeting of key conformational states and novel paths to destabilize aggregates for applications of TA2. In parallel, novel high-throughput small animal models (e.g. *C. elegans*, *Drosophila*, zebrafish, yeast) may enable more effective early screens.

To leverage knowledge from currently siloed fields and maximize impact across insufficiently researched rare diseases, as well as highly prevalent but difficult to address disorders, proposers shall develop approaches to measure and modulate protein aggregation to be deployed against one rare (less than one in 100,000) *and* one non-rare disease from the following categories:

1) Neurodegenerative disease
2) Non-neurodegenerative chronic illness (e.g., cancer, diabetes, other peripheral protein folding disorder, etc.).

Submissions must identify the two disease indications including suspected or targeted mechanism of action for their proposed solution, along with recent literature citation(s) and/or evidence supporting the presence of IDR misfolding and/or aggregation in their chosen disease indications.

After proposers have developed candidate modulators of protein folding for at least two chosen indications *in vitro*, proposers shall refine one of those modulators for *in vivo* efficacy and safety studies for their NDD indication in the second phase of BIOGAMI. Proposers must demonstrate efficacy *in vivo* through demonstration of preservation or restoration of protein function and the ability to prevent or reverse protein aggregation. Proposers can select the best animal model and means to demonstrate efficacy, whether disease-specific models or other systems of choice.

Test and evaluation of candidate protein folding modulators may require modifications to or adaptations of TA1 model systems and assays. Proposals should describe the ability of

the model systems to demonstrate discovery and validation of novel IDR modulators generally, as well as the methods by which TA1 model systems would be adapted to assess candidate modulator activity for each of the chosen indications specifically (if required). Proposers should describe the development of tests for qualitative and quantitative detection of protein folded states, as well as detection of restored protein function and/or interactions. For both *in vitro* and *in vivo* studies, proposers should describe methods for detecting off-target effects of protein folding modulators.

The BIOGAMI program is agnostic to the method(s) by which modulators influence IDR folding and aggregation. Novel modulators may be small molecules, peptides, enzymes, biologics, etc. and may utilize a wide variety of mechanisms of action, including but not limited to:

- stabilizing IDR conformations that preserve critical functions, while interfering with or preventing oligomerization and aggregation
- disrupting oligomers and aggregates
- stabilizing or enhancing condensate chemistry or other components
- promoting or stabilizing other IDR interactions

Additionally, proposers shall leverage high-throughput screening of engineered IDR sequences, computational simulations of molecular dynamics, and/or novel assays to identify novel indicators of IDP misfolding and/or aggregation that have potential for clinical applicability in humans. For example, indicators could be exogenous sensors that bind specific aberrant conformations leading to a readable signal, or indirect reporters of protein misfolding and aggregation i.e., loss of downstream protein function. Novel sensors and/or biomarkers must be indicative of downstream protein misfolding and aggregation and may include, but not limited to intermediate IDP conformations, oligomers, membraneless organelles, biomolecular condensates, or protein-nucleic acid complexes, etc.

Potential novel indicators may or may not be determined prior to proposal submission and may be discovered during Phase 1 of BIOGAMI. Ideally, sensors/biomarkers discovered and validated during BIOGAMI could be utilized in a clinical setting for detection of protein misfolding or aberrant IDR behavior at the earliest stages of disease, enabling clinicians to utilize the indicator as a risk stratification metric or as an early screening indicator to support intervention via preventative care. Indicators discovered or designed through BIOGAMI may also have potential use as a predictive tool for evaluating therapeutic response or for use as a surveillance metric for monitoring progression of disease over time.

Proposers should include experimental details of how potential novel indicators will be discovered or designed. Assays for detection may include, but not limited to novel signal amplification steps, biosensors, extraction methods, and/or imaging techniques. Proposers should also include details on methods to refine signal-to-noise ratio, methods

to reduce false positives and negatives, and details regarding use of algorithms or weighting elements if an index/scoring system is to be used.

Assays and analytical methods for detection of ≥1 novel indicator(s) must be validated in appropriate *in vivo* or organoid models of disease as well as validated in appropriate bio-banked or autopsy biospecimens collected from human subjects (e.g., blood, tissue, urine, etc.). By the end of Phase 2, teams should be prepared to engage in a pre-Letter of Intent meeting in preparation of submission of a Biomarker Qualification Letter of Intent to the FDA. Metrics for indicator development can be found in Table 3.

2.3 BIOGAMI DOWNSELECTION & PHASE II PROGRESSION

The BIOGAMI program has established detailed quantifiable and qualitative program metrics for each TA in Tables 2 and 3 with phase-specific metrics to ensure performers succeed as they progress toward a viable platform that can inform development of novel therapeutic classes modulating protein folding and biomolecular condensate formation.

ARPA-H may request performer data as deemed necessary throughout the program to validate technical progress. The performer's progress will be evaluated in alignment with the program metrics outlined in Section 2.4 Technical Area Metrics and will be used to assess success within each phase by BIOGAMI's Program Manager (PM). Failure to meet the metrics within each phase may result in down-selection from BIOGAMI. Additionally, any performer that does not meet the open-source model, commercialization, dangerous gain of function research prevention, and attendance requirements may not progress to the subsequent phase.

Continuation into Phase II will be determined by ARPA-H and will be based on technical progress made in prior phases and available funding.

2.4 TECHNICAL AREA METRICS

At the time of submission, proposers must propose to meet all milestones and metrics for each TA in the timelines as outlined below by phase. ARPA-H will meet with BIOGAMI performers monthly to review progress towards the metrics and milestones defined below. Achievement of all metrics as agreed to by ARPA-H is part of the basis for initiation of moving to the next phase. Key overall program metrics and milestones are listed in the section below.

TABLE 1: Overall BIOGAMI Program Goals	
Strategy	• Address challenges to predicting IDR structure, protein misfolding and aggregation, condensate formation, function and contribution to disease.

	• Develop novel protein folding sensor tools and therapeutics through modulating IDR folding
General Goals	
Open-Source Model	Proposers must outline a plan to culminate in a model for Open-Source access to the foundational assets created by TA1 specifically, inclusive of both the models and datasets.
Commercialization	• A commercialization plan for the solutions designed in TA2 should be developed to lay the path for future pre-clinical work • Teams are strongly encouraged to demonstrate an active partnership with a designated commercial entity at the time of proposal.
Dissemination	Disseminate new technology, models, documents, and other findings to the public and stakeholders through appropriate collaborations with private and government organizations (i.e., patient advocacy groups, and academic institutions).
Attendance and Participation	A 90% mandatory attendance policy in program meetings will establish accountability and a positive, competitive yet collaborative environment.

The technical metrics per phase in TA1 and TA2 are outlined in Tables 2 and 3 below.

Table 2. TA1 Metrics - Establish the molecular grammar of IDRs

Phase	Task	Metrics and Deliverables
Phase 1 (Months 1-24)	**Task 1** Establish high-throughput experimental screening platforms to assess IDR biology (Month 1-12)	High-throughput validation models must (Month 1-12): • Include cell-free, *in vitro*, and/or *in vivo* systems • Allow for rapid measurement of biomolecular condensate formation, aggregation, and protein function/protein-protein interactions • Scale to 10^2-10^4 targets in triplicate to include sequence variants, post-translational modifications, and variable conditions (i.e., temperature, pH, oxidative stress).
	Task 2 Model, predict and	Models can be trained on both natural and

	experimentally/computationally validate IDR structure(s) and dynamics in homogeneous and heterogeneous contexts (e.g., multidomain proteins, nucleic acid interactions, post-translational modifications, environmental conditions) (Month 1-12)	synthetic IDR sequences. Datasets must include IDR domains >35 amino acids long, and total protein length >100 amino acids.
	Task 3 Model, predict and experimentally/computationally validate IDR aggregation and biomolecular condensate formation based on sequence features, post-translational modifications, environmental conditions (Month 1-24)	Models must achieve high predictive accuracy measured by Area Under the Receiver Operating Characteristic curve **(AUROC >0.80)** Performers must determine **kinetics** of liquid-liquid phase separation and solid aggregate formation (e.g., rates of phase separation, diffusion, and transition from liquid condensate to aggregate).
	Task 4 Define IDR interactome based on primary sequence, mutations, and proteoforms (Month 1-24)	Performers must characterize at minimum 10^2-10^4 intrinsically disordered protein (IDP) **complexes** (engineered or native) consisting of the following types of interactions: - protein-protein - protein-RNA - protein-DNA - protein-small molecule Characterized IDP complexes may include those that result in a variety of downstream cellular processes including but not limited to the following: - transcription regulation - chromatin regulation - nuclear transport - liquid-liquid phase separation - intra- or inter-cellular signaling - DNA repair - programmed cell death - membraneless organelle formation - pathological aggregation IDP complex assays may include assessment of binding, downstream cellular processes, and/or phenotypic screens to determine impact of primary sequence, mutations, and proteoforms on the IDR interactome.

		Performers must incorporate interactome characterizations into a computational model to enable predictions of the types of interactions possible based on primary sequence, mutations, and proteoforms.
	Task 5 Initiate validation of TA1 computational models with TA2 target proteins (Month 1-24)	During Phase 1, prediction and validation of target protein properties (IDR structure, dynamics, biomolecular condensate formation, aggregation, and interactome informing protein function) should take **<90 days**.
Phase 2 (Months 25-48)	**Task 5 (continued)** Validate TA1 computational models with TA2 target proteins, with a higher level of predictive accuracy	Performers must meet/exceed the requirements of TA1 Phase 1 (**AUROC > 0.90**) By end of Phase 2, prediction and validation of target protein properties (IDR structure, dynamics, biomolecular condensate formation, aggregation, and interactome informing protein function) should take **<60 days**.

Table 3. TA2 Metrics – Modulate IDPs to detect and control protein folding

Phase	Task	Metrics and Deliverables
Phase 1 (Months 1-24)	**Task 6** Refine *in vitro* and/or *in vivo* validation model systems for use in identifying candidate molecules to detect and modulate protein misfolding and aggregation of two protein targets (Month 7-24)	Refined model systems must: • **Recapitulate protein misfolding** and achieve clinically relevant aggregation, biomarkers, and/or endpoints at >ten-fold higher throughput relative to established disease model Reproduce phenotypic endpoints (e.g., localization, enzymatic activity) with variation across independent experiments of **<15%**
	Task 7 Identify candidate molecules that bind to target protein conformational states and prevent or reverse aggregation *in vitro* against at least **one rare and one non-rare disease** from the two categories below (at least two total indications) (Month 13-24): • **Neurodegenerative disease** • **Non-neurodegenerative**	Performers must demonstrate correlation between indicator levels and 1) protein dysfunction and 2) toxicity relevant to disease ($r>0.6$) Performers must demonstrate preservation or restoration of **>50% critical protein function(s) *in vitro***. If protein function is poorly understood for a target, performer shall demonstrate preservation or restoration of >50% protein

	chronic illness (e.g., cancer, other peripheral protein folding disorder)	interactions as predicted by TA1 models.
Phase 2 (Months 25-48)	**Task 8** Preliminary indicator assay/analytical detection development and identification of candidate indicators for early detection of protein misfolding and/or aggregation in chosen disease indications from Task 7 (Months 25-36):	(Task 8.1) Performers must adapt assays and analytical methods for detection of early indicators of protein misfolding in disease for application in complex biological samples/matrices including samples collected from organoid disease models and/or *in vivo* preclinical disease models. Performers must demonstrate ability to detect **at least 1** novel indicator in complex biological matrices for **both disease indications** as determined in Task 7. (Task 8.2) Additionally, performers must collect biorepository – and autopsy-validation data from human biospecimens for candidate indicator identification and validation for potential clinical utility. Performers must choose **at least 1 disease + novel indicator pair to test in human samples.** The novel indicator must be detectable in human samples with the following criteria: • At least **50 positive test cases** and **50 age-matched control samples** must be evaluated • Positive detection of indicator in **>50% of test cases** • Diagnosis of disease must be confirmed in positive test cases • Indicator levels should correlate with clinical severity of disease over time (preferably through leveraging samples collected longitudinally)
	Task 9 Refine candidate molecules and demonstrate efficacy *in vivo*. 9.1 Continue identification of candidate molecules that detect and halt, reverse, or prevent aggregation in **at least two chosen indications** (Month 25-36) 9.2 Focus development on **one**	Candidate therapeutic molecules must preserve or restore **>90% critical protein function(s) *in vitro* and *in vivo*.** Performers must demonstrate the ability to control protein folding (prevent or reverse protein aggregation) in **animal models** for performer-chosen target (Month 48). **Performers shall initiate safety screening**

	chosen NDD indication in consultation with ARPA-H sponsor and commercial interest. The chosen disease indication should balance factors such as preliminary *in vitro* results, commercial potential, patient impact, etc. (Month 37-48)	**studies**: investigate off-target activity and demonstrate best practices as outlined by the FDA for scientific rigor/reproducibility for novel modulators of protein folding and aggregation.
	Task 10 Refine and validate assays for indicator detection (Month 37-48)	Performers shall refine assays and analytical methods for detection of **≥1 novel indicator** in appropriate *in vivo* and/or organoid models of disease. Assays shall meet the following criteria: • **AUROC > 0.80** • Significant positive correlation between indicator presence and downstream disease progression/regression based on treatment. **Interaction term, p < 0.05** • Novel indicator must be detectable **prior** to detection of standard/established pathological biomarkers in appropriate disease model. • Time to novel indicator detection should be **at least ½** the time to standard pathological biomarker detection in appropriate disease model. Proposers should engage with the FDA in a pre-LOI meeting in preparation for submission to the Biomarker Qualification Program. Performers shall prepare materials for submission of a Biomarker Qualification Letter of Intent to the FDA with the following criteria defined: • Proposed Context of Use • Drug Development Need • Biomarker Information (i.e., type, matrix, category) • Mechanistic Plausibility • Indexing/scoring/statistical/algorithm scheme (if applicable) • Biomarker Measurement Information (i.e., analytical methodology, sensitivity, specificity, accuracy)

2.5 DATA MANAGEMENT AND SHARING PLAN (DMSP)

BIOGAMI proposers must agree to openly share deidentified/sanitized data acquired through TA1 activities during the period of performance. Any member of the scientific community should have access to the data within a year of final data generation and as part of any resulting publications; registration to a specific repository website is acceptable, but approval needs to be automatic. The specific repository where data will be deposited will be chosen in agreement with the ARPA-H PM.

Proposers must submit a Data Management and Sharing Plan (DMSP) as described below within a full proposal (See Appendix E). The proposers will need to present explicit solutions to address the significant data storage and computing challenges presented by the program, with the understanding that the plans and repository may change later in the program.

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

1. Data Type
2. Related Tools, Software and/or Code
3. Standards
4. Data Preservation, Access, and Associated Timelines
5. Access, Distribution, or Reuse Considerations
6. Oversight of Data Management and Sharing

Within the DMSP, proposers must include a detailed plan of what types of TA1 data, platforms, or portions of platforms they will be sharing with the scientific community as a result of the program. The proposal should provide a detailed plan for curating publicly available protein structures/structural ensembles, biochemical assays, and functional data relevant to the program.

In addition, proposers must provide an explicit plan for timely material, data, and platform exchange between all team members on the proposal, as the free flow of information is critical for the success of the predictive platform development and its verification. The data should be transmitted frequently, in a timely manner, and in its entirety. The development of universal cell-free, *in vitro*, and *in vivo* high-throughput experimental systems for assessing IDR dynamics by TA1 and their dissemination will require performers to prepare plans for sharing and distribution of non-data resources that will be generated by the proposed project, including cell line origin, experimental tools and specifications, protocols, biomaterials, and reagents.

Data and platforms generated in TA2, (i.e. indication-specific *in vitro* and *in vivo* systems, modulators of protein folding, *de novo* IDR sequences, novel biomolecular condensates), are not required for inclusion in the DSMP. Rather, there are no data sharing responsibilities for any data produced in performance of TA2.

2.6 COMMERCIAL AND REGULATORY REQUIREMENTS

The ARPA-H mission is to improve health outcomes for all Americans, and a significant part of improving outcomes is bringing innovations to market. To this end, BIOGAMI has a series of commercial development milestones that performers are required to meet. These milestones will help ensure that preclinical development of BIOGAMI platforms and therapeutic candidates ideally position the performers for clinical and commercial success following the conclusion of the BIOGAMI program.

Prior to award, all proposing teams must submit 5-year and 10-year commercialization plans, with specific requirements for each BIOGAMI TA (see **Table 4**).

Table 4. Commercialization Requirements

Commercialization Requirements	
Commercialization Plan	A draft commercialization plan for the therapeutic and indicator solutions designed in TA2 should be developed in the proposal to lay the path for future pre-clinical work. Revisions to the commercialization plan must be submitted prior to the end of Phase I (Month 21) with established commercial relationship (see below).
Translation Advisory Board	To ensure transition of BIOGAMI technologies and assets, performer teams must convene a Translation Advisory Board. The Board must consist of >3 members, and can consist of expertise from Office of Technology Transfer, venture capital, consultants, or industry partners among others. Proposals should provide intended Board member area(s) of expertise, and the Board should be finalized by month 6. ARPA-H resources from the Office of Commercialization can be leveraged to identify specific individuals for inclusion. The Board should meet at least annually, and should help advise the Commercial Partnership.
Commercial Partnerships	Teams are strongly encouraged to demonstrate an active partnership with a designated commercial entity at the time of proposal. The active partnership must be supported by documentation, including but not

	limited to a Letter of Interest, Memorandum of Understanding, or term sheet. If a team is a consortium of all non-commercial entities, a clear commercialization plan addressing the challenges of this approach must be proposed and progression to Phase 2 will require establishing a relationship with a commercial entity/pharmaceutical company, including but not limited to a Letter of interest, Memorandum of understanding, or term sheet by month 21.

2.7 REQUIREMENT ON PREVENTING DANGEROUS GAIN OF FUNCTION RESEARCH

To date, prion diseases are the only examples of protein misfolding disorders that are transmissible between individuals. Prion research under the BIOGAMI program is considered within scope only as it relates to model prions that do not cause disease. Therefore, research on any known disease-causing prions both with human or agricultural impact are not permitted in this program (including bovine spongiform encephalopathy, scrapie and chronic wasting disease, among others).

Further, any research that could result in increased prion or prion-like agent transmissibility between species or alter the host range or tropism of such agents may be considered Dangerous Gain Of Function (DGOF) per Executive Order 14292 and are not permitted in this program.

Activities that could be considered Dangerous Gain of Function research and are thus unacceptable include:

1. Any research that may increase the transmissibility of a prion or prion-like agent between species
2. Any research that may alter the host range or tropism of a prion or prion-like agent
3. Any research that enables prion-like infectious transmission or increases seeding and spreading of misfolded and/or aggregated Intrinsically Disordered Proteins between individuals within or between species
4. Any research on known disease-causing prions with human or agricultural impact

If the proposed research will involve prions or prion-like agents, proposers must additionally submit appropriate risk mitigation documentation including but not limited to Standards of Practice (SOPs), training, etc.

Development of assays will be for the express purpose of identifying therapeutic (not exacerbating factors) for aggregation. Proposers must acknowledge that if discoveries are

made that show potential enhancement of aggregation, such conditions or leads will be immediately aborted and reported to the PM.

As part of the data sharing and open-source strategy, proposers must outline a plan to ensure publicly shared datasets, algorithms, or experimental findings that do not offer methods for optimizing protein folding or aggregation toward functions with malicious or destructive use potential.

Proposers must complete Appendix I for DGOF questionnaire to address any potential Dangerous Gain of Function risk.

Through up-front and on-going assessments, selected BIOGAMI performers will be required to flag any results of concern with the ARPA-H PM as they arise during the program. BIOGAMI Performer PIs will be responsible for communicating DURC/DGOF prohibited activities to all team members, and for establishing reporting channels within the team.

2.8 GENERAL REQUIREMENTS

Multi-Party Team Requirements

The BIOGAMI program is seeking unique multi-party teaming arrangements that enable teams to perform dynamically by bringing together the diverse expertise required for the program's varying phases and aspects. Unlike a traditional prime/subperformer arrangement where the prime performer is the leader of the team throughout the program, the multi-party teaming structure allows different members of the team to take the lead role at different stages of the program life cycle based on expertise and experience. The structure of a performing team and its teaming arrangement must be able to accommodate this type of change in project leadership over the course of performance, allow for open communication between the Government and all performers on a team, and ensure that all team members are responsible for performance and invested in the success of the program.

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

The multi-party team does NOT need to be established as a separate legal entity as the teaming agreement (also sometimes called articles of collaboration) serves to bind all members to the team. Should the team choose to incorporate or establish some form of legal entity in the future, that is their choice but doing so or not will not affect their selectability.

A key strength of the multi-party teaming structure is that it allows for direct interaction by the Government with all members of the team, ensures that members are independently and collectively responsible for successful performance, and enables seamless leadership changes as the project evolves. For convenience, the team generally chooses one member to act as the agent and/or lead member who often handles administration and reporting duties on behalf of the team. For example, although the Government contract is between the multi-party team and the government, the agent will often sign the contract on behalf of the team. Additionally, the agent is usually the direct payee, receiving funds from the Government and distributing payment to team members.

The multi-party teaming agreement does not need to be in place at the time of proposal. However, proposals must include a clear organizational structure that highlights anticipated leadership transitions throughout the program. ARPA-H will not dictate the structure of the team, beyond the minimum requirements detailed below. At a minimum, the proposer teaming structure must:

1. Not be a prime/subperformer structure. Solution summaries/proposals submitted in this structure will be rejected as non-conforming. However, teams may subcontract with commercial vendors and consultants not performing an essential component of the program project.
2. Identify an organization to perform administrative functions and act as an agent for the team. The agent organization does not need to be the lead performing organization, but the agent must also perform substantive technical work on the program project beyond program management and administrative functions. Regardless, the Government must be free to interact with any team members not just the agent and/or lead performing organization.

If selected as a BIOGAMI performer, the proposing team must execute the multi-party teaming agreement prior to award. The teaming agreement must detail the team structure, roles, and responsibilities and bind the team members to the agreement. All members of the team must be parties to a single other transaction award with the government. Whatever the team structure, the lead performing organization must be able to change during performance or between phases. The teaming agreement must account for the full scope of the BIOGAMI program. The Government is not a party to and will not approve the teaming agreement. The Government must have evidence that the teaming agreement has been executed in order to make an award to the team.

ARPA-H recognizes that this approach may be unfamiliar or new to many performers. ARPA-H strongly encourages performers who are interested in a deeper explanation of

this approach and how it can be fully utilized by teams to attend the BIOGAMI Proposers' Day and ask any questions they may have.

Reporting Requirements

Monthly Technical and Financial Status Reports and Meetings

Performance reporting will be required throughout the program, and will include:

- Monthly technical and financial status reports for discussion with the ARPA-H PM team.
- Monthly meetings which can be virtual, of at least 1 hour to discuss results, underlying science, project challenges and solutions, and other project-related topics.
- Performer and sub-performer data, as deemed necessary throughout the program to validate technical progress.

Attendance at the meetings must include the performer PI and project manager; however, ARPA-H may request members of performer teams to attend these meetings as it deems necessary. ARPA-H may also elect to hold ad hoc site visits at performer and sub-performer locations, as agreed upon by the performer team. Attendance at all meetings will be recorded and is expected to be no less than 90% annually.

ARPA-H may alter the cadence of such reports and meetings and may request additional Performer data as deemed necessary to evaluate technical and non-technical progress as deemed necessary. Other U.S. government stakeholders may participate at Performer portfolio reviews to provide feedback to the ARPA-H PM Team.

Annual Meetings

BIOGAMI anticipates convening annually for PI review meetings. The PI from each performer team (with additional key personnel at the discretion of the PI) will be required to present research progress in person at program review meetings. The purpose of these reviews is to ensure adequate engagement with the ARPA-H team to discuss progress towards milestones and scientific goals and any ongoing technical or programmatic challenges that must be overcome to achieve the overarching goals of the program.

The government team will also visit the performer site(s) at least once per year. Performers should provide in-depth technical and programmatic updates, as well as facility tours, for the government team during the site visit. Details for the site visit agendas and reports will be in collaboration with the ARPA-H PM and performers.

3. ELIGIBILITY INFORMATION

3.1 ELIGIBLE PROPOSERS

All responsible sources capable of satisfying the Government's needs may submit a proposal to this ISO. Specifically, universities, non-profit organizations, small businesses and other than small businesses are eligible and encouraged to propose to this ISO.

While there is statutory language that may suggest ARPA-H is limited in the number of awards it may make to one entity, there are circumstances in which ARPA-H may make more than three awards to a particular person or entity. ARPA-H encourages entities to submit their research ideas notwithstanding this perceived limitation. Any proposal received will be fairly considered for award and, if it is of interest to ARPA-H, will be selected for an award.

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

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

- FFRDCs and Government entities, including federal Government employees, are not permitted to respond to this ISO as a member of a performer team.
- If an FFRDC or Government entity has a unique research idea that is within the technology scope of this ISO that they would like considered for funding; OR, if an FFRDC or Government entity, including a federal Government employee, is interested in working directly with the Government team supporting the research described by this ISO, contact BIOGAMI@arpa-h.gov.
- If a potential performer believes an FFRDC has a unique capability without which their solution is unachievable, they may provide documentation as part of their Solution Summary submission demonstrating they have exhausted all other options. ARPA-H will consider the documentation to determine if inclusion of the FFRDC is necessary for the Solution.

Current Professional Support

Those individuals/entities currently providing contracted support services to ARPA-H have an organizational conflict of interest (OCI) that cannot be mitigated and thus are ineligible for award.

Non-U.S. Entities

ARPA-H will prioritize awards to entities (organization and/or individuals) that will conduct funded work in the United States. Non-U.S. entities may participate to the extent that such participants comply with any necessary nondisclosure agreements, security regulations, export control laws, and other governing statutes applicable under the circumstances. In accordance with these laws and regulations, in no case will awards be made to entities organized under the laws of a covered foreign country [as defined in section 119C of the National Security Act of 1947 (50 U.S.C. Ch 44 § 3059)]; a foreign entity of concern meeting any of the criteria in section 10638(3) of the CHIPS and Science Act of 2022; an individual that is party to a malign foreign talent recruitment program, as defined in Section 10638(4) of the CHIPS and Science Act of 2022; or entities suspended or debarred from business with the government.

3.2 SYSTEM FOR AWARD MANAGEMENT (SAM)

All proposers must have an active registration in SAM.gov for their proposal to be found conforming. Proposers must maintain an active registration in SAM.gov with current information at all times during which a proposal is under consideration or a current award from ARPA-H is held. Information on SAM.gov registration is available at SAM.gov.

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

4. SUBMISSION PROCESS

4.1 SUBMISSION PROCESS OVERVIEW

Submissions for BIOGAMI are as follows:

- ✓ **Step 1:** Submit Solution Summary (Proposers are encouraged / discouraged to move to Step 2).
- ✓ **Step 2:** Submit Full Proposal (Proposers may submit full proposals, regardless of whether encouraged or discouraged in Step 1).

4.2 SOLUTION SUMMARY SUBMISSIONS

Solution Summary submissions are REQURIED and are due by March 4, 2026. See Appendix A for the required Solution Summary format.

4.3 FULL PROPOSALS

Full proposal submissions are due by the date listed in the ISO Summary Information Section on page 4. See Appendix B for the required Full Proposal format. Full proposals are to consist of the following:

Volume I, Technical and Management Proposal	
Volume Element	**Page Limit**
Cover Page	1
Executive Summary	30, See Formatting Instructions Below
Solution Fit with BIOGAMI	
Technical Plan	
Management Plan	
Capabilities	
Commercialization Plan	
Task Description Document (TDD)	N/A, See Appendix C
Schedule and Milestones – GANTT Chart	N/A, See Appendix D
Data Management and Sharing Plan (DMSP)	N/A, See Appendix E
References	N/A

Volume II, Cost Proposal	
Volume Element	**Page Limit**
Cost Proposal Spreadsheet(s), including for subcontractors at any tier	N/A, See Appendix F
Cost and Pricing Data Support documents, including a Cost Narrative	N/A, See Formatting Instructions in Appendix B

Volume III, Administrative and Policy Requirements Submission	
Volume Element	**Page Limit**
Team Member Identification and associated Biographical Common Forms and Current and Pending (other) Support Common Forms	N/A, See Appendix G
FFRDC Participation	
OCI Affirmations and Disclosure	
Research Security Disclosure	
Novelty of Proposed Work	
Intellectual Property (IP)	
Human Subjects Research	
Animal Subjects Research	
Representations Regarding Unpaid Delinquent Tax Liability or a Felony Conviction Under any Federal Law	
Cybersecurity	
Biosecurity	
Security Attestation Form	N/A, See Appendix H
Dangerous Gain of Function Assessment	N/A, See Appendix I
Draft OT Response	N/A, See Appendix J

4.4 SUBMISSION INFORMATION

All submissions in response to this ISO must be written in English and must be consistent with the content and formatting requirements of corresponding appendices.

Proposers are responsible for submitting all written submissions via the ARPA-H Solution Submission Portal and ensuring receipt by the date and time specified in the ISO—*with the exception of the Intent to Propose*—which should be submitted by e-mail to BIOGAMI@arpa-h.gov. No other method of submission is permitted.

Account registration is required to submit via the ARPA-H Solution Submission Portal and

account registration may take several business days to process. Plan to register an account well in advance of the solution summary submission deadline as late submissions resulting from delays with registration may not be accepted or considered.

4.5 PROPRIETARY INFORMATION

Proposers are responsible for clearly identifying proprietary information in any submissions. 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.

ARPA-H is responsible for handling submissions in accordance with applicable federal law, including the Freedom of Information Act (FOIA).

5. SUBMISSION REVIEW AND EVALUATION PROCESSES

5.1 CONFORMING SUBMISSIONS

Conforming submissions contain all requirements detailed in this ISO. Submissions that fail to include required information may be deemed non-conforming and may be removed from further consideration and/or rejected without further review. A submission may be deemed non-conforming under this ISO if it fails to meet one or more of the following ISO requirements:

- The proposed concept is applicable to the BIOGAMI program.
- The proposers meet the eligibility requirements.
- The submission meets the submission requirements.
- The submission 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).
- Submission does not fall under Dangerous Gain of Function research as determined by the DGOF Assessment (See Appendix I).

Proposers will be notified of non-conforming determinations via email correspondence.

Please note that ARPA-H reserves the right, at its discretion, to reject proposals as non-conforming if they are determined to be duplicative of previously submitted solution summaries and proposals under this or any other ARPA-H ISO.

5.2 REVIEW PROCESS

Solution Summary Review

ARPA-H will review and respond to all proposers submitting Solution Summaries. Solution Summaries will undergo an initial review and provide potential proposers with feedback on whether ARPA-H is interested in the proposed solution/concept. Solution Summaries that are outside the scope of the research and development (R&D) ISO will not be evaluated further. The response will indicate whether a proposer is encouraged or discouraged from submitting a proposal. Although potential proposers may submit a proposal regardless of the feedback provided in response to a Solution Summary, ARPA-H Solution Summary feedback is provided to ensure that potential proposers are making an informed decision on the investment of time and resources to a full proposal. Feedback will be provided to the administrative and technical points of contacts noted on the solution summary cover page.

Proposal Review

ARPA-H will conduct a scientific and technical review of each conforming full proposal. Proposals will be evaluated using Evaluation Criteria #1 – #4, listed in descending order of importance and how well the submission meets the criteria stated in this ISO. At a minimum, proposers will be provided with notification of the Government's decision on whether the proposal was selected for negotiation of an award. Notification of the Government's decision will be provided to the primary technical point of contact included in the ARPA-H Solution Submission Portal.

5.3 EVALUATION CRITERIA FOR PROPOSALS

All proposals will be evaluated using the following evaluation criteria, listed in descending order of importance.

CRITERIA 1: Overall Scientific and Technical Merit

The proposed technical approach is innovative, feasible, and complete. Comprehensive technical approach and granular technical elements provided are complete and in a logical sequence with all proposed deliverables clearly defined such that an outcome that achieves the goal can be expected as a result of the award. The proposal identifies major technical risks and planned mitigation efforts are clearly defined and feasible. 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: Proposer's Capabilities and/or Related Experience

The proposed technical team has the expertise and experience to accomplish the proposed tasks; the proposer's prior experience in similar efforts clearly demonstrates an ability to deliver products that meet the proposed technical performance within the

proposed budget and schedule; the proposed team has the expertise to manage the cost and schedule and; similar efforts completed/ongoing by the proposer in this area are fully described, including identification of other Government entities (see Section 3.1).

In terms of capability, the Government shall assess the Volume III bio-sketches provided for the performer team members including the Principal Investigator, Project Manager, Commercialization Experts, and any other key personnel on the project team as requested by ARPA-H.

CRITERIA 3: Potential Contribution to Relevance to the ARPA-H Mission and User Experience

Proposals will be evaluated on the potential future Research & Development, commercial, and/or clinical applications of the project proposed, including whether such applications may have the potential to address areas of currently unmet need within biomedicine and improve health outcomes; the degree to which the proposed project has the potential to transform biomedicine; and/or the potential for the project to take an interdisciplinary approach.

CRITERIA 4: Assessment of Proposed Cost/Price

All proposals will be evaluated to determine the reasonableness or value of the estimated price/cost proposed to accomplish the work in the Task Description Document (TDD). Analysis may be performed to ensure proposed costs (1) are realistic for the proposed scientific and technical approach and capabilities/related experience; (2) accurately reflect the technical goals and objectives of the solicitation; (3) are consistent with the proposer's TDD and (4) reflect a sufficient understanding of the costs and effort needed to successfully accomplish the proposed technical approach. The costs for the proposer teams should be substantiated by the details provided in Volume II of the proposal (e.g., the type and number of labor hours proposed per task, the types and quantities of materials, equipment and fabrication costs, travel and any other applicable costs including the basis for the estimates) – See Appendix B for further instructions.

It is expected the effort will leverage all available relevant prior research to obtain the maximum benefit from the available funding. For efforts with a likelihood of commercial application, appropriate resource sharing may be a positive factor in the evaluation.

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

5.4 RESEARCH SECURITY REVIEW (RSR)

ARPA-H will conduct RSRs, per ARPA-H's Research Security Program, on proposals that have been approved for funding negotiations. The RSR process is not a part of the

agency's scientific and merit review process, but documentation submitted at time of proposal is utilized for RSRs. Awards will not be made until ARPA-H completes the RSR process for that proposal.

5.5 HANDLING COMPETITION SENSITIVE INFORMATION

It is the intent of ARPA-H to protect all proposals as competitive sensitive information and to disclose their contents only for the purpose of evaluation, and only to screen personnel for authorized reasons, in accordance with applicable federal laws and regulations, including the Freedom of Information Act (FOIA). Despite any restrictive notices, submissions may be handled by ARPA-H support contractors during the evaluation process for administrative purposes and/or to assist with technical evaluation.

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

5.6 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. If warranted, portions of resulting awards may be segregated into pre-priced options. In the event the Government desires to award only portions of a proposal, negotiations will commence upon selection notification. The Government reserves the right to fund proposals in phases or with options for continued work, as applicable.

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 Agreements Officer (AO) will have sole discretion to negotiate all terms and conditions with proposers. 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.

6. POLICY REQUIREMENTS AND MISCELLANEOUS OTHER INFORMATION

6.1 CONTROLLED UNCLASSIFIED INFORMATION (CUI) ON NON-FEDERAL INFORMATION SYSTEMS

Please include a response to the below in Volume III (CUI disclosure):

Access to Sensitive Data.

Does this proposed project involve controlled unclassified information (CUI) as defined by 32 CFR § 2002 and/or sensitive personal and/or health data as identified in 28 C.F.R Part 202 that, if compromised or corrupted, could have a negative impact on U.S. national and/or economic security?

Data categories in 28 CFR Part 202 include:
(1) covered personal identifiers;
(2) precise geolocation data;
(3) biometric identifiers;
(4) human genomic data;
(5) personal health data; and
(6) personal financial data.

1-The proposed project **does not/will not** involve processing, storing, and/or transferring CUI and/or sensitive personal and/or health data as identified in 28 CFR Part 202.

2-It is unknown if proposed project **does/will** involve processing, storing, and/or transferring CUI and/or sensitive personal and/or health data as identified in 28 CFR Part 202.

3-The proposed project **does/will** involve processing, storing, and/or transferring CUI and/or sensitive personal and/or health data as identified in 28 CFR Part 202.

6.2 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.

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.

Agency Supplemental OCI Policy

ARPA-H restricts Performers from concurrently providing professional support services, including Advisory and Assistance Services or similar contracted support services, in addition to performing as an R&D technical Performer. Therefore, the Proposer must affirm whether it or any proposed team member (proposed subawardee, etc.) is providing professional support services to any ARPA-H office(s) under: (1) a current award or subaward; or (2) a past award or subaward that ended within one calendar year prior to the proposal's submission date.

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

- The name of the ARPA-H office receiving the support,
- The prime contract number, and
- Identification of proposed team member (including any proposed subawardee) providing the support.

Proposers shall follow the instructions in, and complete, Appendix G, to be submitted through Volume III, to address the requirements of this ISO Section.

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 must provide additional documentation as requested for Senior/Key Personnel for ARPA-H to determine the existence of any risk. The format for this submission can be found in the Administration and National Security Document Template (Appendix G).

6.3 INTELLECTUAL PROPERTY

Proposers must 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 and should be aligned with the level of government funding provided to generate and/or develop the IP.

Proposers shall follow the instructions in, and complete, Appendix G, to be submitted through Volume III, to address the requirements of this ISO Section.

6.4 HUMAN SUBJECTS RESEARCH

A proposal for funding that will involve engagement in human subjects research (HSR) (as defined in 45 CFR § 46) must provide documentation of one or more current *Assurance(s) 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 HSR must be reviewed and approved by an Institutional Review Board (IRB), as applicable under 45 CFR § 46 and/or 21 CFR § 56. The entity's HSR 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 ARPA-H funded work. This includes, but is not limited to, laws, regulations, and policies regarding the conduct of HSR, 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 HSR 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 HSR training by all investigators and key personnel who will be involved in the design or conduct of the ARPA-H funded HSR. Funding cannot be used toward HSR until ALL approvals are granted.

Proposers shall follow the instructions in, and complete, Appendix G, to be submitted through Volume III, to address the requirements of this ISO Section.

Human subjects research is **not** anticipated for the BIOGAMI program. Use of previously collected/deidentified human samples for validation of TA2 is not considered human subjects research provided that samples are collected under an approved IRB protocol and already deidentified prior to acquisition by the performer.

6.5 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) shall comply with the laws, regulations, and policies on animal acquisition, transport, care, handling, and use as outlined in:

- 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); and,

- 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).

The Proposer must complete and submit the Vertebrate Animal Section worksheet for all proposed research anticipating Animal Subject Research (ASR).

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.

Proposers shall follow the instructions in, and complete, Appendix G, to be submitted through Volume III, to address the requirements of this ISO Section.

6.6 ELECTRONIC INVOICING AND PAYMENTS

Performers will be required to register in, and submit invoices for payment through, the Payment Management Services (PMS) https://pms.psc.gov.

6.7 GENOMIC DATA SHARING

A resulting award will include the requirement to comply with NIH's Genomic Data Sharing (GDS) Policy (NOT-OD-14-124). Information about the GDS policy can be found at: https://grants.nih.gov/grants/guide/notice-files/NOT-OD-24-157.html.

6.8 PROCUREMENT OF SYNTHETIC NUCLEIC ACIDS OR BENCHTOP SYNTHESIZERS

Beginning April 26, 2025, HHS funds may only be used to procure synthetic nucleic acids or benchtop nucleic acid synthesis equipment from sources adhering to the Office of Science and Technology Policy Framework for Nucleic Acid Synthesis Screening. HHS awardees are expected to adhere to the Office of Science and Technology Policy Framework for Nucleic Acid Synthesis Screening for HHS projects.

Proposers shall complete Appendix G, to be submitted through Volume III, as it relates to

this ISO Section.

6.9 GOVERNMENT-FURNISHED PROPERTY/EQUIPMENT/INFORMATION

Government-furnished property/equipment/information may be provided to selected performers. Include any planned Government-furnished property/equipment/information in Volume III.

6.10 DRAFT OT RESPONSE

An initial draft of the ARPA-H agreement for this effort has been made available on SAM.gov. The proposer must include a copy of the draft agreement with any redlines, comments, and/or proposed edits to ARPA-H as a part of the proposal package. If no redline, comments, and/or edits are proposed, the proposer must provide a written statement that there are no proposed changes. There is no page limit for this document. The document must be in .pdf, .odx, .doc, or .docx format. See Appendix J for Draft OT.

6.11 LIST OF APPENDICES

Appendix A: Solution Summary Format and Instructions

Appendix B: Full Proposal Format and Instructions

Appendix C: ARPA-H Task Description Document (TDD)

Appendix D: ARPA-H GANTT Chart Sample

Appendix E: Data Management and Sharing Plan

Appendix F: ARPA-H Cost Proposal Spreadsheet

Appendix G: Administrative & National Policy Requirements Document - Template for Other Transaction (OT) Agreement

Appendix H: ARPA-H Security Attestation Form

Appendix I: Dangerous Gain of Function Assessment

Appendix J: ARPA-H Draft Other Transaction Agreement