Functional Repair of Neocortical Tissue (FRONT)
Health Science Futures (HSF)
Innovative Solutions Opening (ISO) ARPA-H-SOL-25-120
July 10, 2025

TABLE OF CONTENTS

Table of Contents....2
1 ISO Summary Information....3
2 The Program....4
2.1 ISO PURPOSE....4
2.2 INTRODUCTION....5
2.3 PROGRAM OVERVIEW....6
2.4 TECHNICAL AREAS AND PROGRAM STRUCTURE....7
2.5 PROGRAM GOALS AND TECHNICAL AREA METRICS....10
2.6 GENERAL REQUIREMENTS....15
3 Eligibility Information....16
3.1. ELIGIBLE PROPOSERS....16
3.3. SYSTEM FOR AWARD MANAGEMENT (SAM)....17
4 Submission Process....17
4.1. SUBMISSION PROCESS OVERVIEW....17
4.2. SUBMISSION INFORMATION....18
4.3. SUBMISSION DEADLINES....19
4.4. PROPRIETARY INFORMATION....19
4.5. FUNDING RESTRICTIONS....19
4.6. QUESTIONS AND ANSWERS....19
5 Application Review....20
5.1 EVALUATION CRITERIA....20
5.2 REVIEW OF SOLUTION SUMMARIES AND FULL PROPOSALS....21
6 Award Administration....22
6.1.1 SOLUTION SUMMARY REVIEW PROCESS....23
6.1.2. FULL PROPOSAL REVIEW PROCESS....23
6.2. EVALUATION AND AWARD DISCLAIMERS....23
6.3. REPORTING....24
7 Policy Requirements and Miscellaneous Other Information....24
7.1. ORGANIZATIONAL CONFLICTS OF INTEREST (OCI)....24
7.2 INTELLECTUAL PROPERTY....25
7.3. HUMAN SUBJECTS RESEARCH....25
7.4. ANIMAL SUBJECTS RESEARCH....26
7.5. ELECTRONIC INVOICING AND PAYMENTS....26
7.6. GOVERNMENT-FURNISHED PROPERTY/EQUIPMENT/INFORMATION....26
8 APPENDIX A: SOLUTION SUMMARY FORMAT AND INSTRUCTIONS....27
9 APPENDIX B: FULL PROPOSAL FORMAT AND INSTRUCTIONS....31
10 APPENDIX C: TARGET PRODUCT PROFILE GUIDELINES....47

1 ISO SUMMARY INFORMATION

FEDERAL AGENCY: Advanced Research Projects Agency for Health (ARPA-H), Health Science Futures Office.

PROGRAM TITLE: Functional Repair of Neocortical Tissue (FRONT)

ANNOUNCEMENT TYPE: Initial Announcement

INNOVATIVE SOLUTIONS OPENING: ARPA-H-SOL-25-120

DATES: (All times listed are Eastern Time)

- **Posting Date:** July 10, 2025
- **Proposers' Day:** August 8, 2025, 9:00 AM to 5:00 PM
- **Questions & Answers (Q&A) Due Date:** August 27, 2025, 5:00 PM
- **Solution Summaries Due:** August 18, 2025, 5:00 PM
- **Full Proposals Due:** September 25, 2025, 5:00 PM

PROGRAM SUMMARY:

FRONT will pioneer a curative therapy for the more than 20M adults in the US living with chronic neocortical brain damage from neurodegeneration, stroke, trauma, and other causes, which costs the country an estimated $800 billion per year. Worldwide, more than 200M people live with debilitating after-effects of brain damage.

Current treatments for neocortical damage are limited to physical, occupational, speech, and psychological therapy, which have only partial success, leaving many patients unable to regain the abilities they lost. FRONT will develop a first-in-class tissue replacement therapy intended to restore function. FRONT will leverage the field's deep understanding of neocortical tissue development, which includes high resolution data from single cell transcriptomics and proteomics, protocols for deriving brain cells from induced pluripotent stem cells (iPSC), demonstrations in pre-clinical studies of the potential for new neocortical neurons to integrate with the adult neocortex, successful clinical trials for brain cell therapies, and new companies breaking ground in the manufacturing of cell and tissue products.

Although academic and industry labs have studied the effects of cell and organoid transplants into the brain, no effort thus far has engineered a complete tissue graft with the proper cytoarchitecture, cell types, and extracellular components necessary to achieve normal tissue maturation, internal wiring, and effective integration with host brains after transplantation. FRONT will address this challenge with coordinated efforts from experts across the necessary disciplines, including developmental neurobiology, human iPSC biology, computational biology, tissue engineering, neurosurgery, electrophysiology, and systems neuroscience.

FRONT will be divided into two (2) technical areas as follows: 1) Defining and generating commercially viable graft tissue through iPSC-derivation of all neocortical precursor cell types, identification of major extracellular components, and generation of graftable early-stage neocortical precursor tissue ex vivo; 2) Optimizing grafting in the adult neocortex, with high resolution outcome measures comparing in-vivo differentiated graft tissue with natural tissue, including analyses for cell type ratios, densities, positions, vascularization, tissue structure, neural connectivity, and the encoding of useful information to the host in a large animal model. The result of a successful FRONT program will be readiness for human trials.

In brief, FRONT will take the "permanent" out of brain damage – leading to restoration of function for hundreds of millions of patients with limited or no current treatment options.

Brain tissue restoration has ethical, legal and social implications (ELSI) which require careful consideration as part of the development of new technologies. While many closely related issues are under active consideration by the broader cell, tissue and organ replacement community, the capabilities developed through this program place these considerations in new contexts. To this end, FRONT will support ELSI work in several ways. First, the Program Management team intends to make ELSI-related expertise available to performer teams to assist in identifying and addressing relevant issues. Performers will be expected to devote meaningful effort to these ELSI elements of their work including developing mechanisms for patient engagement and feedback. Similarly, there may be new challenges in meeting regulatory standards for clinical use that require working closely with ARPA-H and regulatory bodies to potentially establish new standards.

Outside studies and guidance including the National Academy of Science's (NAS) 2021 "The emerging field of human neural organoids, transplants, and chimeras; science, ethics, and governance", and the Organization on Economic Co-operation and Development's (OECD) "Neurotechnology Toolkit" will inform the ARPA and Performer teams' work.

Notably, FRONT aims to restore natural tissue function without the use of human embryos or fetal tissue. Therefore, FRONT will not consider proposals that include either the use of human embryonic or fetal tissue, the use of human-animal chimeric tissue, or whose aim deviates from restoring natural neocortical function.

ANTICIPATED INDIVIDUAL AWARDS: Multiple awards are anticipated.

POTENTIAL AWARD INSTRUMENTS: Other Transaction Agreements (OT).

COST SHARING: Cost sharing is not required but it may be proposed where appropriate.

AGENCY CONTACT: All inquiries shall be sent to FRONT@arpa-h.gov

2 THE FRONT PROGRAM

2.1 ISO Purpose

This publication constitutes a merit-based process in accordance with 42 U.S.C. § 290c. Any resultant award negotiations will follow all pertinent laws and regulations.

The mission of ARPA-H is to accelerate better health outcomes for everyone by advancing innovative research that addresses society's most challenging health problems. Awardees will develop groundbreaking new ways to tackle health-related challenges through high potential, high-impact biomedical and health research. ARPA-H seeks to accomplish the FRONT goals as described in this ISO package. Ultimately, ARPA-H intends to negotiate multiple OT Agreements with proposers whose proposals are most advantageous to the Government.

It is important to note that specifically excluded are proposals that: 1) offer incremental improvements to the existing state-of-the-art, 2) make use of human embryos or human fetal tissue, or human-animal chimeras, 3) do not address cost of goods, manufacturability, and product quality, 4) do not address the objectives of the program, 5) direct policy changes, traditional education and training, or center coordination and construction of physical infrastructure, which are outside the scope of the ARPA-H mission. Furthermore, all proposals must comply with all relevant HHS regulations on research and pre-clinical studies using human stem cells:

https://stemcells.nih.gov/research-policy/guidelines-for-human-stem-cell-research

https://osp.od.nih.gov/wp-content/uploads/QA_Chimera_Policy_updated_1_Feb_2017.pdf

2.2 Introduction

FRONT is seeking to eliminate the permanent deficits caused by brain damage through regenerative grafts that can restore the structure and function of the adult neocortex. Stroke, trauma, neurodegeneration, tumors, and other forms of injury can all cause permanent brain damage, most often to the neocortex. Traditional approaches to treating patients with moderate to severe damage are limited to physical, occupational, speech, and psychological therapy. Despite these best efforts, most patients with severe damage cannot regain the abilities they have lost. In addition, promising recent results suggest that neurostimulation of sub-neocortical motor pathways may help amplify or circumvent the upper cortical motor damage to provide patients with more motor control. However, such approaches will not be readily applicable to all neocortical functions and will not offer patients complete functional recovery. This leaves patients dependent on costly care for the rest of their lives, often with large financial and emotional burdens placed on loved ones and caregivers. The annual cost in the United States of treating stroke patients alone exceeds $80 billion, with the cost expected to triple within the decade. FRONT, once clinically translated, holds the potential to benefit an estimated 20 million Americans who currently live with a disability as a result of brain damage, and for whom there are yet no effective treatment options.

The aim of FRONT is to develop a first-in-class neocortical precursor tissue that accurately emulates the structure, cellular composition, and function of early human neocortical tissue, and that once surgically grafted and differentiated can replace damaged tissue. This will enable

millions of individuals with what is currently considered permanent brain damage to regain lost functions, such as motor control, vision, and speech.

We invite applications that leverage in-depth knowledge of normal human brain development to obtain a neocortical precursor-like tissue that can be grafted, that matures on its own in situ, and that integrates with the host brain in a way that allows it to encode information that is useful for its recipient. The success of FRONT will bring relief to millions of Americans afflicted with brain damage that would otherwise be considered permanent.

2.3 Program Overview

To date, efforts to develop cortical grafts, despite showing high levels of short and long-range connectivity with their hosts and certain functional features, have failed to demonstrate functional replacement, defined as graft-derived circuits encoding useful information to their host. Functional replacement will minimally require tissue structure, tissue composition, and levels of synaptic integration within and across the graft boundary that are similar to normal neocortical tissue.

The achievement of FRONT's goal is facilitated by extensive previous work that has mapped in detail many early cellular and molecular pathways essential for neocortical development. This work has provided an unprecedented understanding of the cells and molecular cues needed for normal maturation of the human neocortex. Combined with foundational iPSC differentiation protocols, tissue generation techniques, high resolution cell and connectivity mapping, and methods for measuring and manipulating neuronal activity and assessing its role in behavior, FRONT will establish the first neocortical precursor tissue graft with normal cell populations and cytoarchitecture that matures in vivo into normal neocortical tissue that is functionally integrated with the host.

Recent research has drastically improved the depth and breadth of our understanding of the structure, function, and early development of the neocortex. Several recent scientific developments and new technologies are now enabling a comprehensive molecular and cellular approach to producing functional neocortical grafts:

1. In addition to a deep understanding of human neocortical tissue development, the development of the neocortex has been mapped at high resolution with transcriptomics.

2. Extracellular structure of tissues and cell-cell interactions can be further characterized by proteomics.

3. Human iPSCS have been used to produce most or all of the precursor cell types required for generating neocortical tissue with a full complement of mature cell types.

4. Neurons derived from transplanted neocortical neural precursor cells and organoids have been demonstrated to connect electrophysiologically with the host brain, even with distant targets.

5. Established principles of neuroplasticity indicate that new (untrained) neocortical tissue will be incorporated and used to re-encode lost functions or maintain existing ones that would otherwise degenerate.

FRONT will support multidisciplinary teams to develop and test graftable tissue that closely mimics natural neocortical precursor tissue. The graftable tissue might include a full complement of iPSC-derived precursor cell types, including those for vascular, fibroblastic, neural, and glial subtypes, and extracellular components deduced from multi-omics analysis that together are necessary post-grafting for normal tissue survival, structure, maturation, and function. Preclinical testing of graft tissue will include but is not limited to optimization of surgical procedures in adult hosts, immunohistological stains, single cell transcriptomics, vascular function, connectomics, non-invasive monitoring of graft survival and differentiation, neuronal electrophysiology, and tests for information encoding using opto- or chemogenetic tools in the context of a learned behavior. Grafting procedures and graft integration will be developed and tested in adult small and large animal models using at least one model of focal disease in a large animal model. As an alternative to assembling the graftable neocortical precursor tissue from base cellular and extracellular components, the program is also open to generating similar tissue from other novel approaches, so long as the tissue meets regulatory standards for clinical use. For all approaches, the goal is to have by the end of the program a product that meets FDA regulatory standards for safety and efficacy and is ready for investigational new drug (IND) filing and clinical trials. Additionally, proposals should have a strong ethical, legal, and social implications component (see 2.5.2 Ethical, Legal, and Social Implications (ELSI) Requirements below).

FRONT will revolutionize how we think about brain damage and bring hope to tens of millions of Americans as well as hundreds of millions globally who suffer the after-effects of brain damage and have few if any effective treatment options.

2.4 Technical Areas and Program Structure

2.4.1. Technical Areas (TAs)

In order to achieve a functional cortical graft, FRONT will enlist teams that each propose to address all milestones in *both* of the two (2) technical areas (TAs). These TAs cover specific technical developments needed for a successful functional neocortical tissue replacement, including graft tissue generation, effective engraftment procedures, restoration of function via graft neuronal activity, and FDA readiness. Along the development pathway, FRONT teams will organize their effort over three (3) sequential phases that will each conclude with critical milestones and decisions.

Specifically, the TAs are:

TA1: Production of graft precursor tissues.

TA2: Optimization of surgical engraftment procedures, as measured by: TA2a, neuronal and vascular integration; and TA2b, graft function.

Technical Area 1 (TA1): Precursor tissue

Proposals should consider generating an ex vivo neocortical precursor tissue that emulates natural early neocortical tissue comprised of neural and pre-pial layers, with a possible nascent marginal zone. With the addition of inhibitory and hem precursors, precursor tissues that mimic this age range could contain all the human iPSC (hiPSC)-derived age-appropriate precursor cell types, structure, and developmental cues required to mature on their own when grafted (in TA2) into a tissue with all the cell types found in the mature neocortex and overlying pia (as determined by unbiased omics analyses). The structure and cell-cell contacts of the precursor tissue should also match its natural counterpart, where consideration should be given to recapitulating key extracellular structural and signaling factors (based on omics analyses) to get tissue maturation off on the right foot. Proposers should consider initiating genetic modifications of hiPSCs that would be useful in the preclinical tests in TA2 (for example, in neurite tracing, neuronal silencing) during TA1. Successful completion of TA1 will result in a graftable neocortical precursor tissue that emulates natural tissue and that meets regulatory standards for clinical use.

Technical Area 2 (TA2): Grafting and outcomes

Proposals should consider initiating the optimization of surgical engraftment prior to completing precursor graft assembly in TA1, for example by testing protocols with placeholder tissue, or real precursor tissue from rodents or larger mammals with gyrified neocortices. In optimizing surgical engraftment, variables to consider include time of grafting after lesion (with respect to inflammatory/scarring state), the space needed for graft growth (which should match normal growth of natural precursor tissue into more mature tissue), choice of pre-clinical animal model (e.g. gyrified brains would allow gyrus replacement, whereas mammals such as rodents with smooth brains do not provide this option despite other advantages). The development of novel surgical tools and methods for precise orientation, handling, and adhesion of the implanted tissue should also be considered. Tissue implants may be as small as 1mm in diameter by 200um thick, but will grow as large as 1cm^3 – presenting unique challenges for successful implantation and maturation that must be considered. Therefore, consider initial optimization in rodents for graft survival, structural integrity, and early cell-type analyses, transitioning to gyrified models for analyses of more mature graft features (connectivity, physiology, and information encoding).

Performers must test the graft in a disease model with focal damage to a primary cortex (e.g. V1, M1), and may optionally perform tests in models of diffuse damage, where grafts could be introduced into more associative cortical areas, so long as clear and meaningful metrics for graft-derived function are provided. Successful completion of TA2 will result in the demonstration that the precursor tissue developed in TA1, when grafted, reproducibly generates new tissue that resembles normal tissue, that is vascularly and neuronally integrated with the host brain, and that can encode useful information to its host. Successful completion of TA2 also includes clinical readiness.

Work under TA1 and TA2 will be divided into three (3) phases. Phase I will comprise graft tissue development, good manufacturing practice (GMP) iPSC banking, and initial optimization of

surgical procedures. Phases II and III will focus on ensuring engraftable precursor tissue is GMP, establishing the reproducibility of surgical engraftment and integration, and demonstrating safety and efficacy in small and large animal models including a focal disease model, resulting in IND readiness. Advancement into subsequent phases will be determined by the government program manager and based on success in prior phases, ability to meet future metrics/milestones, and availability of funding. A proposal must consider and provide information on each of the following aspects.

Phase I Teams will start by generating precursor tissues. By mid-Phase I (12 months) performers engineering human neocortical precursor tissue must demonstrate that they can obtain all cellular components from iPSCs and source all omics-identified extracellular components necessary to begin testing tissue assembly, while performers using other approaches must achieve a neocortical precursor tissue matching that of early-stage natural tissue. Performers will also have initiated the optimization of engraftment techniques. Continuation in Phase I will be dependent on the success of precursor tissues against required metrics (see Figure 1 showing TA1 metrics and down selection timeline in Section *2.4.2 Program Structure and Options* below).

Please note that human iPSCs will be generated from adult skin or blood cells that are de-differentiated in the lab.

By the end of Phase I (24 months), performers will have validated a neocortical precursor tissue at high omics resolution and with other metrics (see TA1 metrics below), will have generated a GMP iPSC cell bank with a sufficient number of cells to be used preclinically and in clinical trials, will have continued the optimization of the engraftment procedure now including as a readout rapid vascularization, and will have generated the tools required to characterize the anatomical and physiological connectivity as well as functional features of grafts matured in vivo. Continuation to Phase II will be dependent on the success of precursor tissues against required metrics (see TA1 metrics and down selection timeline below).

Phase II Teams will advance Phase I developments towards IND enabling studies by formalizing validated fabrication procedures into regulatory compliant (GMP) procedures. Further, teams will perform in-depth characterization of graft integration in small and large animal models as well as establish a large animal model of brain injury for graft testing. By mid-Phase II (36 months), teams must have demonstrated high engraftment efficiency and rapid vascularization and have trained large animal subjects on a neocortical-dependent behavioral task that will be used to measure the ability of graft-derived neurons to encode useful information to their host. Continuation in Phase II will be decided based on the success of engraftment and a demonstrated behavioral paradigm for testing graft function against required metrics (see TA2a and TA2b metrics and down selection timeline below).

By the end of Phase II (48 months), performers will have a GMP process in place for generating the neocortical precursor tissue; will have thoroughly characterized the structure, anatomical connectivity, physiological connectivity, and certain functional features of mature grafts in small and large animal models; and will have initiated the lesioning, grafting, and monitoring of grafts in subjects for behavioral experiments in TA2b.

Continuation to Phase III will be decided based on the success of grafts in these areas against required metrics (see TA2a and TA2b metrics).

Phase III (12 months) Teams will complete behavioral studies aimed at demonstrating the ability of new graft-derived tissue to encode useful information to its host and will complete Initial Targeted Engagement for Regulatory Advice on CBER products (INTERACT) and pre-IND discussions with the FDA.

2.4.2 Program Structure and Options

The FRONT program is structured as a 5-year effort consisting of three (3) phases, as shown in Figure 1.

- Phase 1: 24 months
- Phase 2: 24 months
- Phase 3: 12 months

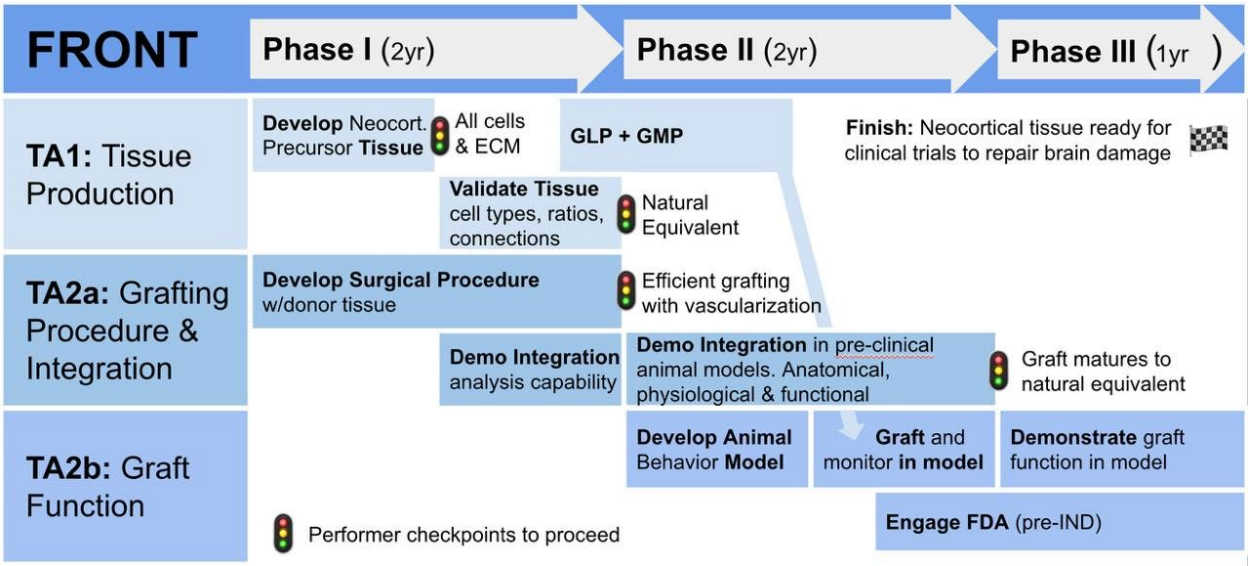

Figure 1: Figure illustrating the program structure, including TAs, Phases, and checkpoints.

Performers should consider initiating TAs and Phases earlier than the timelines outlined in this ISO when possible.

2.5 Program Goals and Technical Area Metrics

2.5.1 Program Goals and Technical Metrics

The overall FRONT program goals are shown in **Table 1**. The expected metrics are listed in **Table 2**: TA1 (Precursor Tissue Production) Metrics and Objectives and **Table 3:** TA2 - Graft integration. In addition to meeting the goals and metrics, proposers will be required to attend FRONT meetings and provide the following plans and profile:

- Ethical, Legal and Social Implications Plan

- Clinical Trial Plan
- Commercialization Plan including working with ARPA-H and the FDA on ensuring regulatory standards are met or developed.
- Target Product Profile (APPENDIX C: TARGET PRODUCT PROFILE GUIDELINES)

Table 1. Overall Program Goals

Overall Program Goals
1. Clinical ready precursor tissue capable of integrating with the host brain and encoding useful information, which meets FDA regulatory standards.
2. Demonstrated therapeutic effects from implanted grafts including recovery of learned behaviors.
3. Plan for ensuring developed technologies meet ARPA-H commitments to regional availability and low costs, including short and long-term strategies to reduce costs from fabrication to transplantation.
4. Plan for performing teams and ARPA-H to address Ethical Legal and Social Implications (ELSI) of their work, including standards around use, potential for misperceptions and misuse, and compliance with relevant HHS regulations on research and pre-clinical studies or needs to address ambiguities therein, and mechanism for patient engagement. This must include requirements listed in the ELSI requirements section.
5. Comprehensive commercialization strategy detailing initial disease target(s), multi-stage clinical trial plan, projected costs by phase, etc.
6. Regulatory framework defined in collaboration with ARPA-H consistent testing requirements to verify quality and safety of future graft products.
7. Unified understanding of patient needs and perspectives to maximize the clinical impact of FRONT and minimize misperceptions regarding brain surgeries and brain tissue grafts.
8. Attendance at all FRONT meetings (as outlined below).

Technical Area Metrics

Table 2: TA1 (Precursor Tissue Production) Metrics and Objectives

TA1 - Phase 1	
IPSC protocols for precursor cells	1. Generate GMP human iPSC master bank. 2. All human precursor cell types with **>99%** cell lineage-relevance (by ICC, qPCR, scRNAseq).
Extracellular Components (n/a for Alternates to Engineered Tissue)	1. Omics identification & validation of top 10 ECM & signaling factors by proteomics, IHC, ELISA, etc. 2. Development of biogels liquid at 0-25oC, gel at 37oC, and support vascularization from iPSC-derived endothelial cells, and polarization of neocortical precursor cells.
Alternates to Engineered Tissue	Advanced developmental mimetics to generate appropriate age neocortical precursor tissue.

Validation of Precursor Tissue	1. All cells are human with **>95%** cell viability. 2. Cell type ratios, densities, and layering **±10%** natural tissue. 3. Extracellular components within **±10%** natural tissue. 4. **>95%** polarized radial glia attached to basement membrane.
Deliverables	1. Mid-Phase 1: Have cells+ECM OR alternative advanced developmental mimetic tissue source. 2. End-Phase 1: Validated precursor tissue (normal structure, cell types, ratios, contacts); GMP iPSC master bank.
TA 1 - Phase 2	
Transport/storage	Identify transportability & storage conditions with ≥85% viability.
Graft manufacturing	1. GMP manufacturing of neuronal, vascular, glial, and pial precursor cells (≥**20M/type**). 2. GMP manufacturing of ECM and tissue.
Safety in vivo	in vivo safety studies in large animals.
Pre-IND documents	1. Pre-IND documentation for **CMC** (chemistry, manufacturing, and controls). 2. Finalized **QA/QC** protocols.
Deliverables	1. Phase 2: GMP protocols set, IND-ready precursor tissue.

Table 3: TA2 - Graft integration

TA2a - Phase 1 – With Animal Donor Tissue	
Efficiency of engraftment	1. **>85%** (within **±20%** expected size after 30d) engraftment efficiency in preclinical models, including a disease model. 2. Complete comparison of **autologous, matched, allogeneic, and xenogeneic** outcomes in a pre-clinical large animal model.
Graft vascularization	Graft vascularization within 2 days of transplantation, vascular density and branching within 10% of natural at 1 month, blood-brain barrier formation within 3 months.
Engraftment Validation Method Development	Have started method development and demonstrated capability to test: • Tissue structure and anatomical neural connectivity • Physiological neural connectivity • Characterize functional features
Deliverables	1. A surgical method that reproducibly leads to engraftment of animal donor precursor tissue with rapid vascularization. 2. Demonstrate capability to measure structure, anatomical and physiological wiring within itself and with the host brain.
TA2a - Phase 2 – With Engineered Tissue:	

Efficiency of engraftment	**>85%** (within **±20%** expected size after 30 days) engraftment efficiency in preclinical large animal models, including a disease model.
Graft vascularization	Graft vascularization within **2 days** of transplantation, vascular density and branching within 10% of natural at 1 month, BBB formation within **3 months**.
Structure and anatomical neural connectivity	Anatomical connectivity (intra graft and graft-host; pre- and post-synaptic) **>70%** of native during maturation and once mature.
Physiological neural connectivity	Electrophysiological connectivity (intra graft and graft-host; pre- and post-synaptic): **>70%** of natural over 1, 3, 9 months.
Characterize functional features	Functional features (e.g. response to external stimuli for visual grafts, evoked movement for motor grafts), >50% natural.
Deliverables	• **Mid-Phase 2:** A surgical method that reproducibly leads to engraftment of the precursor tissue with rapid vascularization. • **End-Phase 2:** Graft that achieves normal anatomical and physiological wiring within itself and with the host brain.

Table 4: TA2 - Graft integration

TA2b - Phase 2 and Phase 3	
Train large animals on behavioral task	Subjects score >90% accuracy on cortical-based behavioral task.
Lesion, graft, monitor, retraining	1. Lesion results in loss of **>80%** ability to perform task in pre-trained subjects. 2. Non-invasive monitoring (**MRI, ultrasound**) reveals the presence of healthy graft throughout study. 3. Retraining upon graft maturation results in **>70%** reacquisition of task accuracy compared to pre-lesion, and one standard deviation greater compared to non-grafted control.
Graft function via silencing	Silencing method (e.g. chemogenetically) blocks activity of **>50%** of graft neurons and results in a significant – and transient – drop in task accuracy.
FDA preparations	After consultation with regulatory experts, have completed **INTERACT and pre-IND** meetings with FDA.
Deliverables	1. **End Phase 3**: New neocortical tissue that can encode useful information to its host, and that can be applied clinically.

Definitions: iPSC (induced pluripotent stem cell), FACS (fluorescence-activated cell sorting), qPCR (quantitative polymerase chain reaction), scRNAseq (single cell RNA sequencing), QA (quality assurance), QC (quality control), GLP (good laboratory practice), GMP (good manufacturing practices), CMC (chemistry, manufacturing, and controls), 3D (three-

dimensional), IND (investigational new drug), INTERACT (INitial Targeted Engagement for Regulatory Advice on CBER producTs).

The metrics and timelines as outlined in the above tables will increase in difficulty and complexity over the course of the FRONT program. Monthly technical and financial status reports will be required and discussed with the ARPA-H Program Manager at monthly meetings. ARPA- H may request performer data as deemed necessary throughout the program to validate progress toward achieving the program's goals.

At the time of submission, proposers **must**:

- Propose to meet all milestones and metrics for each TA in the timelines outlined in the Phases.

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

- Monthly technical and financial status reports for discussion with the ARPA-H Program Manager team.
- Weekly check-ins, which can be virtual, of at least 1 hour to discuss results, underlying science, project challenges and solutions, and other project-related topics.
- ARPA-H may request performer and sub-performer data and arrange visits to their facilities as deemed necessary throughout the program to validate technical progress.
- Attendance at the meetings must include the performer PI, project manager, and in addition ARPA-H may request members of performer teams to attend these meetings as it deems necessary.
- A 2-page market research report by the end of year two, a 5-page manufacturing protocol by the end of year four, and an ARPA-H Exit Report, which includes a 2-page clinical trial plan and a 2-page commercialization plan by the end of year five.
- Participation by team leaders in the beginning of Phase 3 in a workshop on FRONT treatment availability organized by ARPA-H, meet quarterly with ARPA-H to develop a plan, and provide an implementation plan (no more than 3 pages) at the end of Phase 3.
- Working in partnership with ARPA-H, performer teams will provide yearly reports detailing their progress made in discussions with the FDA to ensure regulatory standards are met or developed.
- Yearly reports on ELSI-related activities in preparation for meetings with FRONT's team and other experts on ELSI topics for annual Summits on Frontier Solutions for Restoring Neocortical Tissue, which will be organized by ARPA-H.

2.5.2 Ethical, Legal, and Social Implications (ELSI) Requirements

- Performer teams must devote the necessary meaningful effort and resources to establish a plan for addressing ethical, legal and social issues coupled with the uses and potential misconceptions and misuses of the proposed new technology, including pathways to solicit patient and other stakeholder engagement and feedback. Each team must designate in their proposal an ELSI representative that is part of the leadership team. This performer team representative will attend the FRONT Kickoff and will also meet with the FRONT team along with other experts and ARPA-H leads to outline ELSI and patient engagement plans. Each performer team must, within 12 months of Kickoff, file their first ELSI report outlining ELSI considerations, strategies, and outreach plans followed within two weeks by a meeting with the FRONT team and additional experts and within a month a first Summit on Frontier Solutions for Restoring Neocortical Tissue. To continue refining ELSI and patient engagement, yearly reports, meetings with the FRONT team, and participation in Summits on Frontier Solutions for Restoring Neocortical Tissue will be required. ELSI needs and opportunities identified through the teams' work and at these summits will be considered for further funding, if appropriate.

2.5.3 Requirements for making the treatment widely available

ARPA-H is committed to affordable health care for all geographic regions of the country. ARPA-H will review all conforming proposals and performers throughout the program to ensure that metrics and milestones prioritize end-user needs regarding affordability, independent of geographic region.

To address potential misperceptions about the program and educate patients of the benefits of our technology, performers with ARPA-H will actively engage in conversations and workshops with relevant patient advocacy groups on how best to inform and educate patients on the new treatment option.

2.6 General Requirements

2.6.1 Team requirements

Proposals are expected to involve teams with the broad expertise needed to collectively achieve the goals of both TA1 and TA2. Specific content, communications, networking, and team formation are the sole responsibility of the proposer. A group or co-investigator may participate in multiple proposals. It is likely that performer teams will be collaborations between multiple for-profit companies with additional academic institution or NGO collaboration. We encourage performers to leverage the regulatory expertise of product developers.

While ARPA-H expects proposer teams to encompass a variety of organizational types (e.g., commercial organizations, academic institutions, non-profits, etc.), to ensure future commercialization success and adherence to project timelines, performers are encouraged to have or partner with an organization with expertise in commercializing cell and tissue products.

A full-time experienced project manager must be included in the proposed team to ensure efficient communication within and between performer teams, subcontractors, and ARPA-H. Communication with ARPA-H includes organizing and coordinating yearly Summits on Frontier

Solutions for Restoring Neocortical Tissue. A qualification description for the project manager position, whether named or to be hired later, must be included as part of the proposal.

In addition, ARPA-H requires that the proposal designate an ELSI representative to engage the community; however, it is recognized that the needs of the performer team may change over time and as those needs evolve the ELSI representative, or their level of effort, may change. These changes will be considered in consultation with the ARPA-H program manager.

ARPA-H will host a Proposers' Day in support of the FRONT program as described in Special Notice ARPA-H-SN-25-120. The purpose is to provide potential proposers with information on the program, promote additional discussions, and encourage team networking.

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

ARPA-H will not reimburse potential proposers for participation at Proposers' Day (or time and effort related to submission of Solution Summaries, or full proposals).

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, small businesses and other than small businesses, non-profit organizations, and universities 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 organization. ARPA-H encourages organizations 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.

3.1.1. 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, non-profit organizations, academia etc. In certain circumstances, FFRDCs and Government Entities will 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 prime or sub-performer on a proposed 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 FRONT@arpa-h.gov.

- If a potential prime 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.

3.2. 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.

3.3. System for Award Management (SAM)

All proposers must have an active registration in SAM.gov in order for their proposal to be found conforming. Proposers must maintain an active registration in SAM.gov with current information at all times during which a proposal is under consideration or 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

The submission process consists of the following steps:

1. **Proposers' Day (optional):** ARPA-H organized event to allow interested proposers to meet and self-organize into comprehensive teams capable of meeting all FRONT technical and non-technical requirements.
2. **Solution Summary submission:** Required overview of the effort to be proposed summarizing the goals of the proposed work, the research plan, and the team. See Appendix A for the required Solution Summary format.
3. **Review of Solution Summaries:** Based on the evaluation of Solution Summaries, selected teams will be encouraged or discouraged to submit full proposals.

4. **Full Proposal submission:** Required document package comprising a detailed description of the proposed effort, expected outcomes, performing team, timeline, budget, and any supporting materials. See Appendix B for the required Full Proposal format.
5. **Review of Full Proposals.** Based on the evaluation of Full Proposals, proposers may or may not be selected for award negotiations.
6. **Selection/Non-Selection Notification and Award Negotiation.**

4.2. Submission Information

4.2.1 FRONT ISO Package

The official ISO and attachments are those posted on the System for Award Management (SAM) at SAM.gov. This announcement and any references to external websites herein constitute the total solicitation. If proposers cannot access the referenced material posted in the announcement found at https://www.sam.gov/, please contact the administrative contact listed herein.

4.2.2 Content and Form of Submission

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

All solution summaries and full proposals submitted in response to this ISO must be written in English and must be consistent with the content and formatting requirements of Appendix A (Solution Summary Format and Instructions), and Appendix B (Full Proposal Format and Instructions).

Proposers are responsible for submitting all solution summaries and full proposals via the ARPA-H Solution Submission Portal and ensuring receipt by the date and time specified in the ISO. No other method of submission is permitted.

Registration is required to submit via the ARPA-H Solution Submission Portal and registration may take several business days to process. Plan to register well in advance of the solution summary submission deadline as late submissions resulting from delays with registration will not be accepted or considered.

4.2.3. Solution Summary Format

Solution summaries (formerly known as abstracts) are mandatory, and the Government may only consider those submitted by the submission date. All solution summaries submitted in response to this solicitation must comply with the content and formatting requirements in Appendix A. Solution summaries may not exceed four (4) pages, excluding the cover page, Rough Order of Magnitude (ROM), team qualifications, Target Product Profile (TPP), and references. The Government will not review pages beyond four (4) pages. Official transmittal letter is not required.

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

4.2.4. Full Proposal Format

All proposals submitted in response to this ISO must comply with the content and formatting requirements in the applicable Bundle of Attachments templates. Proposers should use the templates provided in the Bundle of Attachments. The Bundle of Attachments includes the following six (6) templates:

1. Tech and Management (30 pages)
2. Task Description Document (TDD) (no page limit)
3. Target Product Profile (TPP) (1 page maximum per TPP; use template),
4. Cost Proposal (no page limit, must include costs devoted to ELSI)
5. Cost Proposal Spreadsheet (fill in applicable tabs; must include ELSI-related costs)
6. Administration & National Policy (no page limit)

Documents requested to be submitted with the templates should be included as attachments to the applicable template (e.g., HSR/ASR documents included as attachments to the Administration & National Policy template, cost back-up as attachments to the Cost Proposal template, etc.). Each template includes instructions for completion.

4.2.3. Administrative and National Policy Requirements

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

4.3. Submission Deadlines

Submission deadlines for Solution Summaries and full proposals are provided in Section 1.

4.4. 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.

4.5. Funding Restrictions

Pre-award costs will not be reimbursed unless a pre-award agreement is negotiated and approved by ARPA-H Agreements Officer prior to award.

4.6. Questions and Answers

All questions regarding this ISO must be submitted to FRONT@arpa-h.gov. ARPA-H will post

Q&As to the ARPA-H ISO Website and SAM.gov on an on-going basis and may not respond directly to email inquiries. All questions must be in English and must include the name, email address, and telephone number of a point of contact, and should be submitted by the Q&A deadline posted with other key dates. Proposers submitting questions to individual Government team members (e.g., Program Manager) should not expect a response.

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.

5 APPLICATION REVIEW

5.1 Evaluation Criteria

ARPA-H will review and respond to all proposers submitting solution summaries. Solution summaries will be reviewed to provide potential proposers with feedback on whether ARPA-H is interested in the proposed solution/concept. At a minimum 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 required to submit a full proposal. Feedback will be provided to the administrative and technical points of contact noted on the solution summary cover page.

Full proposals will be evaluated using Evaluation Criteria #1-5, listed in descending order of importance.

5.1.1. Criteria 1: Overall Scientific and Technical Merit

The proposed technical approach is innovative, feasible, and complete. Task descriptions and associated technical elements provided are complete and in a logical sequence with all proposed deliverables clearly defined such that 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 will potentially impact the Government's ability to transition technology.

5.1.2. Criteria 2: Proposer's ELSI Plan

Plans for addressing ELSI must minimally abide by the requirements outlined in **2.5.2** Ethical, Legal, and Social Implications (ELSI) Requirements.

5.1.3. Criteria 3: Proposer's Capabilities and/or Related Experience

The proposed technical team has the expertise and experience to accomplish the proposed tasks; the proposed team has prior experience in similar efforts which 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 the proposed team similar efforts completed/ongoing by the proposer in this area are fully

described (see Section 3.1.1).

In terms of capability, the Government shall assess the Volume III bio-sketches provided for the performer team members including the PI, Project Manager, key technical personnel, Regulatory and Commercialization experts, and any other key personnel on the project team as requested by ARPA-H (5 pages maximum per team member).

5.1.4. Criteria 4: Relevance to the ARPA-H Mission

ARPA-H's mission is to **accelerate better health outcomes for everyone** by supporting the development of **high-impact solutions** to society's most **challenging health problems**. Proposals will be evaluated on potential future R&D, commercial, and/or clinical applications of the project proposed including whether such applications may have the potential to address areas of unmet need within biomedicine and improve health outcomes; degree to which the proposed project has the potential to transform biomedicine; and potential for the project to take an interdisciplinary approach.

5.1.5. Criteria 5: Assessment of Proposed Cost/Price

All solution summaries and proposals will be evaluated to determine the reasonableness or value of the estimated budget proposed to accomplish the work in the Task Description Document (TDD). An analysis will be performed to ensure proposed costs:

- are realistic for the technical and management approach,
- accurately reflect the technical goals and objectives of the ISO,
- are consistent with the proposer's scope of work, and
- reflect a sufficient understanding of the level of effort needed to successfully accomplish the proposed technical approach.

The costs for the prime proposer and proposed sub-awardees should be substantiated by the details provided in 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).

It is expected the effort will leverage all available relevant prior research to obtain the maximum benefit from the available funding. ARPA-H recognizes that undue emphasis on cost may motivate proposers to offer low-risk ideas with minimum uncertainty and to staff the effort with junior personnel to assume a more competitive posture. ARPA-H discourages such cost strategies.

5.2 Review of Solution Summaries and Full Proposals

5.2.1 Review Process It is ARPA-H policy to ensure impartial and comprehensive Solution Summary/proposal evaluations based on the evaluation criteria listed in Section 5.1 Evaluation Criteria

ARPA-H will conduct a merit based scientific/technical review of each solution summary/proposal. Conforming proposals shall comply with all requirements detailed in this

ISO. Full proposals that fail to include required information may be deemed non-conforming and may be removed from further consideration. Non-conforming submissions may be rejected without further review. A full proposal will be deemed non-conforming under this ISO if it fails to meet one or more of the following ISO requirements:

- The proposed concept is not applicable to the FRONT program.
- The proposers did not meet the eligibility requirements.
- The full proposal did not meet the submission requirements.
- The full proposal did not meet the content and formatting requirements in the attached instructions.
- The proposer's concept has already received funding or been selected for award negotiations for another funding opportunity (whether from ARPA-H or another Government agency).

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

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

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

5.2.2 Handling of 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 screened personnel for authorized reasons, in accordance with applicable federal laws and regulations, including FOIA. Restrictive notices notwithstanding, 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.

6 AWARD ADMINISTRATION

6.1 Selection Notices and Notifications

6.1.1 Solution Summary Review Process

ARPA-H will review and respond to all proposers submitting solution summaries. At that time the proposer will be informed that:

1. ARPA-H discourages the proposer from submitting a full proposal;

2. ARPA-H encourages the proposer to submit a full proposal;

3. ARPA-H will contact the proposer for explanation on any unclear elements in the submitted solution summary in order to determine whether a full proposal will be encouraged or discouraged.

NOTE: All parties, whether encouraged or discouraged to submit a proposal, are eligible to submit a proposal to the FRONT ISO. Solution summaries must be submitted, and feedback received prior to proposal submission. Feedback will be provided to the administrative and technical points of contact noted on the solution summary cover page.

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

6.1.2. Full Proposal Review Process

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

1. ARPA-H has not selected the proposal; or

2. ARPA-H has selected the proposal for funding pending award negotiations, in whole or in part. Official notifications will be sent via email to the Technical POC and/or Administrative POC identified on the proposal coversheet.

3. ARPA-H requires an explanation of any unclear elements in the submitted proposal. Based on that discussion, ARPA-H may not select the proposal or select the proposal in whole or in part and enter into negotiations.

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

Also, as part of the request will be the required National Security documentation to be completed for key personnel on the proposal, and submitted as an Appendix to Volume II, Cost Proposal, of the proposal package.

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

6.2. 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 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 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.

6.3. Reporting

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

7 POLICY REQUIREMENTS AND MISCELLANEOUS OTHER INFORMATION

7.1. 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.

7.1.1. 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 FAR 9.5 disclosure requirement above, a proposer must affirm whether the proposer or any proposed team member (proposed sub-awardee, 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 calendar year prior to the proposal's submission date.

[Proposers shall follow the instructions in and complete Volume III (see Appendix B) 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.

7.1.2. Government OCI Procedures

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

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

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

7.2 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.

NOTE: IP rights assertions will be reviewed under Criterion 1.

7.3. 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 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.

7.4 Animal Subjects Research

All entities submitting a proposal for funding that will involve engagement in animal subjects research (performers 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.

7.5. 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.

7.6. Government-Furnished Property/Equipment/Information

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

8 APPENDIX A: SOLUTION SUMMARY FORMAT AND INSTRUCTIONS

A. General Instructions

All Solution Summaries must use a font type not smaller than 11-point font. Smaller font may be used for figures, tables, and charts (but should be legible). Margins may be no less than 0.5" inch in width. Solution Summaries are limited to four (4) pages, exclusive of a cover page, rough order of magnitude budget, team qualifications, target product profile (TPP), and references. No tables of content shall be provided. The Government may not review pages beyond (4) total; and any Solution Summary submitted that exceeds (4) pages will only be reviewed at ARPA-H's discretion. Solution Summaries should be submitted in a PDF format to ARPA-H Solution Submission Portal. Attachments and embedded links shall not be included. The Solution Summary should address why the proposed idea is relevant to the ARPA-H mission and the proposed FRONT program. Your Solution Summary should address the technical merit of the proposed approach and team organization, capabilities, and qualifications for this proposed idea. Proposers should frame their responses using at least the first 4 of the 10 ARPA-H Heilmeier Questions (HQs):

1. What health problem are you trying to solve? Articulate your objectives using absolutely no jargon.

2. How is it done today, and what are the limits of current practice?

3. What is new in your approach, and why do you think it will be successful?

4. Who cares? If you succeed, what difference will it make?

And include the following items:

- ✓ Team qualifications
- ✓ R&D timeline–what you can accomplish in the agreed upon project timelines?
- ✓ Rough Order of Magnitude (ROM)

B. Cover Page

The cover page should follow the format below. The cover page does not count towards the page limit.

Innovative Solutions Opening	[ISO number]
Solution Summary Title	
Submitter Organization	

Unique Entity Identifier of prime proposer/awardee (UEI), if known	
Type of Organization and website URL if applicable	**Choose all that apply:** Large Business, Other Small Business, Other Educational, or Other Nonprofit
Technical Point of Contact (POC)	Name: Mailing Address: Telephone: Email:
Administrative POC	Name: Mailing Address: Telephone: Email:
Total Estimated Budget	Total: $
Place(s) of Performance	
Other Team Members (sub-performers, including consultants) if any	Technical POC Name: Organization: Organization Type:

C. Proposed Work

Clearly identify the problem(s) to be solved and the outcome(s) sought with the proposed technology concept. Explain the concept's potential to be disruptive compared to existing or emerging technologies including anything with pre-existing funding and how the proposed approach will go far beyond current commercial capabilities.

Describe the final deliverable(s) for the project, one or two key interim milestones, and the overall technical approach used to achieve project objectives. Describe the background, theory, simulation, modeling, experimental data, or other sound engineering and scientific practices or principles that support the proposed approach. Identify adoption challenges to be overcome for the proposed technology to be successful. Describe key technical risks.

D. Target Product Profile

Proposers must include a target product profile (TPP) for the proposed solution for each disease indication (minimum of 2 indications). The TPP should thoughtfully outline the desired characteristics, features, and performance specifications of the product being developed. Target goals with respect to affordability and regional accessibility should be reflective of the best estimates and predictions at the time of writing. General guidelines, examples, and templates of a target product profile, with required key metrics for impact on function and disease indications, are provided (See Appendix C). No more than one page for the TPP, which is not included in the 4-page limit.

E. Team Organization and Capabilities

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

F. Rough Order of Magnitude (ROM)

Please include a ROM to support the proposed project budget as well as the total project cost including cost sharing, if applicable. The ROM should also include a breakdown of the work by fully burdened labor (inclusive of fringe), subcontracts, materials, equipment, travel, other direct costs, indirect costs, profit, cost sharing, and any other relevant costs. Also, estimate the total number of labor hours anticipated per phase in the labor hours row. All subcontracts should total together in the subcontracts line. The below table may be used for this breakdown:

Categories	**Phase I Amount**	**Phase II Amount**	**Phase III Amount**	**Total**
Direct Labor (including fringe)				
Labor Hours				
Subcontracts				
Materials				
Equipment				
Travel				
Other Direct Costs				
Indirect Costs				
Profit/Fee				
Total				

Cost Sharing (if applicable/appropriate)				
Labor hours (in hours)				

Proposers must ensure the ROM encompasses all applicable costs and should modify the above to best reflect the proposer's expected costs. The ROM does not count toward the page limit.

NOTE: Delete all formatting and content instructions prior to submission.

9 APPENDIX B: FULL PROPOSAL FORMAT AND INSTRUCTIONS

Full proposals must follow the guidance in Appendix B. Conforming full proposals should consist of three volumes as follows:

1) Volume I, Technical and Management Proposal

2) Volume II, Cost Proposal

3) Volume III, Administrative and Policy Requirements Submission

Summary of Full Proposal Requirements, including page limits. The following must be used by the prime organization and all subawardees at any tier.

Volume I, Technical and Management Proposal	
Volume Element	Page Limit
Cover Page	1
A. Executive Summary	30
B. Solution Fit with FRONT	
C. Technical Plan	
D. Management Plan	
E. Capabilities	
F. Commercialization Plan	
G. Task Description Document (TDD)	N/A, use provided template/format
H. Target Product Profiles	1 (maximum per TPP), use provided template/format
I. Schedule and Milestones	N/A use provided template/format
J. Data Management and Sharing Plan (DMSP)	N/A (estimated 2 pages)
K. References	N/A
Volume II, Cost Proposal	

Volume Element	Page Limit
Cover Page	1
A. Cost Proposal Spreadsheet(s), including for subcontractors at any tier	N/A, use provided template/format
B. Cost and Pricing Data Support including a Cost Narrative	N/A

Volume III, Administrative and Policy Requirements Submission

Volume Element	Page Limit
Cover Page	1
A. Team Member Identification	N/A, use provided template/format
B. OCI Affirmations and Disclosure	
C. National Security Disclosure and associated biosketches	
D. Novelty of Proposed Work	
E. Intellectual Property (IP)	
F. Human Subjects Research	
G. Animal Subjects Research	
H. Representations Regarding Unpaid Delinquent Tax Liability or a Felony Conviction Under any Federal Law	

The page limitation includes all figures, tables, and charts. All pages shall be formatted for printing on 8-1/2 by 11- inch paper. Margins must be 1-inch on all sides, font size should be no less than 11 point (Arial or non-serif font), and page numbers should be included at the bottom of each page.

Documents must be clearly labeled with the ISO number, proposer organization, and proposal title/proposal short title (in the header of each page). Use the following Title Format: "Volume I_XYZ Institution", "Volume II_XYZ Institution", "Volume II Supporting Documents", etc.

I. Volume I, Technical and Management Proposal

The maximum page count for Volume I is thirty (30) pages, with exclusions as noted in the table above. The cover page and sections G-J below are not included in the page count. However, for all sections, ARPA-H encourages conciseness to the maximum extent practicable. No other supporting materials may be submitted for review. Note that while the Government's evaluation of Volume I against criteria 1-5 is limited to the sections included in the page count limitations, it will be reviewing all sections. The other documents may be used to cross-check the proposal and will also inform feedback for proposers whose full proposals are determined most advantageous and selected for award negotiations.

Volume I should include the following components:

Cover Page

Innovative Solutions Summary	ARPA-H-SOL-25-120
Full Proposal Title	
Prime Awardee/entity submitting the proposal	
Unique Entity Identifier of prime proposer/awardee (UEI)	
Type of Organization and website URL if applicable	**Choose all that apply:** LARGE BUSINESS, OTHER SMALL BUSINESS, OTHER EDUCATIONAL, OR OTHER NONPROFIT (including non-educational government entities) (NOTE: The Small Business Administration's (SBA) size standards determine whether or not a business qualifies as small.). Size standards may be found here: https://www.ecfr.gov/current/title-13/chapter-I/part-121#121.201
Date of Submission	
Technical Point of Contact (POC)	Include salutation Last Name:

	First Name Mailing Address: Telephone: Email:
Administrative POC	Include salutation Last Name: First Name: Mailing Address: Telephone: Email:
Other Team Members (sub-performers, including consultants) if applicable.	Technical POC Name: Organization: Organization Type:
Total funds requested from ARPA-H, and the amount of cost share (if any)	Total: $
Place(s) of Performance	

A. Executive Summary: Provide a synopsis of the proposed project including answers to the following questions:

1. What is the proposed work attempting to accomplish or solve?
2. How is it done today? What are the limitations of present approaches?
    - *What is the competitive landscape?*
3. What are the key technical challenges in your approach, and how do you plan to overcome these?
4. What is new about your approach? Why do you think you can be successful at this time?
    - *Who will benefit from your solution?*
    - *What health outcomes are you accelerating?*
5. Who cares? If you succeed, what difference will it make?

6. What are the risks? Identify any risks that may prevent you from reaching your objectives as well as any risks the program itself may present. Please also describe plans to mitigate these risks at a high level.
7. How much will your project cost?
8. What are your milestones to check for success consistent with FRONT metrics?
9. To ensure access for all regions of the country, how will cost and user experience be addressed in your project?
    - *What is the expected target cost for the product?*
10. How might this program be misperceived or misused (and how can we prevent that from happening)?

B. Solution Fit with FRONT: Clearly describe what the team is trying to achieve and the difference it will make (qualitatively and quantitatively) if successful relative to FRONT's vision and metrics. Provide an overview of the current and previous research and development (R&D) efforts related to the proposed research and identify any challenges associated with such efforts including any scientific or technical barriers encountered during such efforts or challenges in securing sources of funding as applicable. Describe the innovative aspects of the project in the context of existing capabilities and approaches clearly delineating the uniqueness and benefits of this project in the context of the state of the art, alternative approaches, and other projects from the past and present. Describe how the proposed project is revolutionary and how it significantly rises above the current state-of-the-art. Describe the deliverables associated with the proposed project as well as how the project will integrate into existing clinical workflows and successfully improve patient care.

C. Technical Plan: Outline and address technical challenges inherent in the approach and possible solutions for overcoming potential problems. This section should provide appropriate measurable milestones (quantitative if possible) at intermediate stages of the program to demonstrate progress, a plan for achieving the milestones, and a simple process flow diagram of the final system concept. The technical plan should demonstrate a deep understanding of the technical challenges and present a credible (even if risky) plan to achieve the program goal. Discuss mitigation of technical risk.

D. Management Plan: Provide a summary of the expertise of the team including any subcontractors and key personnel who will be doing the work. A PI for the project must be identified, along with a description of the team's organization, including the breakdown by TA. All teams are required to identify a Project Manager/Integrator to serve as the primary POC to communicate with the ARPA-H PM team and OT/Contracts equivalent for each award instrument (e.g., Agreements Officer), coordinate the effort across the team, organize regular performer meetings or discussions, facilitate data sharing, and ensure timely completion of milestones and deliverables. Provide a clear description of the team's organization including an organization chart that includes as applicable: the programmatic relationship of team members; the unique capabilities of team members; the task responsibilities of team members and the teaming strategy among the team members; and key personnel with the amount of effort to be expended

by each person during each year. Provide a detailed plan for coordination including explicit guidelines for interaction among collaborators/subcontractors of the proposed effort. Include risk management approaches. Describe any formal teaming agreements required to execute this program.

E. Capabilities: Describe organizational experience in relevant subject area(s), existing intellectual property, specialized facilities, and any Government-furnished materials or information. Describe any specialized facilities to be used as part of the project, the extent of access to these facilities, and any biological containment, biosafety, and certification requirements. Discuss any work in closely related research areas and previous accomplishments.

F. Commercialization Plan: Briefly outline your current understanding of your technologies target market and the size of that market. Identify 2-3 key competitive technologies operating in the market and their limitations. Outline ownership plans for existing and future IP across the team. Identify ideal partners (e.g. private industry, investors, etc.), that may be pursued to secure funding, manufacturing, and marketing following the award period. Plans shall include completion of the following table:

IP Category (Trade Secret, Patent, or Data)	USPTO# and Docket # and Application #	IP Title	Summary of Intended Use in Project	Asserted rights for Government related to FRONT Program (Government Purpose, Unlimited, Limited.)	Name of Person or Entity Asserting Restrictions (wh o owns the IP?)	Funding Source (Federal Government, other, or Mix**)

G. Task Description Document (TDD): The TDD should provide a detailed task breakdown, citing specific tasks for each TA and their connection to the milestones and program metrics. Each Phase of the program should be separately defined. The TDD must not include proprietary information. Please note the technical proposal must stand on its own as the TDD cannot be used to supplement the 30 pages of the technical proposal.

For each task/subtask, provide:

- A detailed description of the approach to be taken to accomplish each defined

task/subtask.

- Identification of the primary organization responsible for task execution (prime awardee, sub-performer(s), by name).
- A measurable milestone, i.e., a deliverable, demonstration, or other event/activity that marks task completion. Include completion dates for all milestones. Include quantitative metrics.
- A definition of all deliverables (e.g., data, reports, software) to be provided to the Government in support of the proposed tasks/subtasks.

It is recommended the TDD be developed so that each TA and phase of the program is separately defined.

H. Schedule and Milestones: Using the provided format, provide a detailed schedule showing tasks (task name, duration, work breakdown structure element as applicable, and performing organization), milestones, and the interrelationships among tasks. The task structure must be consistent with that in the TDD Measurable milestones should be clearly articulated and defined in time relative to the start of the project.

I. Data Management and Sharing Plan (DMSP) (recommend NTE 2 pages) The DMSP shall include all information included in the 6-Element plan format recommended by the National Institutes of Health (to view the 6-Element suggested format visit https://grants.nih.gov/grants/forms/data-management-and-sharing-plan-format-page). Note this plan will not be specifically evaluated against Criteria 1-5, but will likely be used to inform feedback for proposals who are selected for award negotiations.

J. References: Add a list with the cited literature.

II. Volume II, Cost Proposal

There is no maximum page count for Volume II. The Cost Proposal shall be comprised of the editable Excel Cost Proposal spreadsheet and associated supporting materials ideally provided in a single attachment (e.g., Adobe pdf) led by a Cover page as follows.

Cover Page

Innovative Solutions Summary	ARPA-H-SOL-25-120
Full Proposal Title	
Prime Awardee/entity submitting the proposal	
Unique Entity Identifier of prime proposer/awardee (UEI)	

Type of Organization and website URL if applicable	**Choose all that apply:** LARGE BUSINESS, OTHER SMALL BUSINESS, OTHER EDUCATIONAL, OR OTHER NONPROFIT (including non-educational government entities) (NOTE: The Small Business Administration's (SBA) size standards determine whether or not a business qualifies as small.). Size standards may be found here: https://www.ecfr.gov/current/title-13/chapter-I/part-121#121.201
Technical Point of Contact (POC)	Include salutation Last Name: First Name Mailing Address: Telephone: Email:
Administrative POC	Include salutation Last Name: First Name: Mailing Address: Telephone: Email:
Other Team Members (sub-performers, including consultants) if applicable and type of organization for each	Technical POC Name: Organization: Organization Type:
Total proposed cost separated by base and option(s) (if any)	
Name, address and telephone number of the proposer's cognizant auditor (as applicable)	

Date proposal was submitted	
Commercial and Government Entity (CAGE) Code	
Proposal validity period (Minimum of 120 days)	

A. Cost Proposal Spreadsheet: ARPA-H Standard Excel Cost Proposal Spreadsheet (See Attachment 2). All tabs and tables in the cost proposal spreadsheet should be developed in an editable format with calculation formulas intact to allow traceability of the cost proposal. The cost proposal spreadsheet must be used by the prime organization and all subcontractors at any tier.

While the prime proposer is ultimately responsible for submission of all required documents, sub-performer cost proposal spreadsheets may be submitted directly to the Government by the proposed subcontractor via email to FRONT@ARPA-H.gov. Sub-performer proposals should include Interdivisional Work Transfer Agreements or similar arrangements between the awardee and divisions within the same organization as the awardee.

B. Cost and Pricing Data Support: In addition to using the cost proposal spreadsheet, the cost proposal must include documentation to support the proposed price/budget. Supporting documentation must be in sufficient detail to substantiate the summary cost estimates and should include a description of the method used to estimate costs (e.g., vendor quotes). For indirect costs provide the most current indirect cost agreement (e.g., Colleges and Universities Rate Agreement, Forward Pricing Agreement, Provisional Billing Rates, etc.).

Cost and pricing support may also facilitate a value analysis by the Government through information other than detailed cost and pricing data. Proposers are encouraged to include information related to value-added resources or conditions that are not immediately obvious in the Cost Proposal Spreadsheet or the traditional forms of cost and pricing support information like vendor quotes (e.g., intended intellectual property terms and conditions with perceived future value).

C. Salary Cap: None of the federal funds awarded under this program shall be used to pay the salary of an individual at a rate in excess of the rate identified by the Office of Personnel Management for Executive Level II positions. Nor may the proposed and later negotiated salaries escalate in excess of the Executive Level II rate for the purposes of invoicing for salary support.

Note: The salary rate limitation does not restrict the salary that an organization may pay an individual working under an award; it merely limits the portion of that salary that may be paid with federal funds.

III. Volume III, Administrative and Policy Requirements Submission

Cover Page

Innovative Solutions Summary	ARPA-H-SOL-24-120
Full Proposal Title	
Prime Awardee/entity submitting the proposal	
Unique Entity Identifier of prime proposer/awardee (UEI)	
Type of Organization and website URL if applicable	**Choose all that apply:** LARGE BUSINESS, OTHER SMALL BUSINESS, OTHER EDUCATIONAL, OR OTHER NONPROFIT (including non-educational government entities) (NOTE: The Small Business Administration's (SBA) size standards determine whether or not a business qualifies as small.). Size standards may be found here: https://www.ecfr.gov/current/title-13/chapter-I/part-121#121.201
Technical Point of Contact (POC)	Include salutation Last Name: First Name Mailing Address: Telephone: Email:
Administrative POC	Include salutation Last Name: First Name: Mailing Address: Telephone: Email:
Other Team Members (sub-performers, including consultants) if applicable and type of organization for each	Technical POC Name: Organization:

	Organization Type:
Total proposed cost separated by base and option(s) (if any)	
Name, address and telephone number of the proposer's cognizant auditor (as applicable)	
Date proposal was submitted	
Commercial and Government Entity (CAGE) Code	
Proposal validity period (Minimum of 120 days)	

A. Team Member Identification

[Using the table below as a template, provide a list of all entities as well as specific Key Personnel (PI, Project Manager, other investigators, etc.). Note: Consultants (e.g., 1099s) are considered subcontractors and must be listed.

Prime		
Individual Name:	**Organization:**	Non-U.S. Organization: ☐ Yes ☐ No Non-U.S. Individual: ☐ Yes ☐ No
Sub-Performers, including Consultants		
Individual Name:	**Organization:**	Non-U.S. Organization: ☐ Yes ☐ No Non-U.S. Individual: ☐ Yes ☐ No
Individual Name:	**Organization:**	Non-U.S. Organization: ☐ Yes ☐ No Non-U.S. Individual: ☐ Yes ☐ No

B. Organizational Conflict of Interest Affirmations and Disclosure

a. Are any of the proposed individual team members or their respective organizations (whether prime or subcontractor) currently providing support services to ARPA-H?

☐ No ☐ Yes

b. Did any of the proposed individual team members or their respective organizations (whether prime or subcontractor) provide support services to ARPA-H within one calendar year of this proposal submission?

☐ No ☐ Yes

[If you answered "Yes" to a. OR b., provide the following information for each applicable team member:

- The name of the ARPA-H office receiving the support
- The prime contract number
- Identification of proposed team member (subcontractor) providing the support; and
- An OCI mitigation plan.]

a. Are there any other potential Organizational Conflicts of Interest involving any of the proposed individual team members *or* their respective organizations (whether prime or subcontractor)?

☐ No ☐ Yes

[If yes, provide the following information for each applicable team member:

- Identification of applicable team member; and
- An OCI mitigation plan.]

C. National Security Disclosure

[In accordance with National Security Presidential Memorandum (NSPM)-33 and the associated White House Office of Science and Technology Policy Implementation Guidance, which requires certain individuals to disclose potential conflicts of interest (COI) and commitment (COC), individuals designated as PIs and other senior/key personnel (e.g., Project Manager) under prime and subcontractors are required to complete the Common Form for Current and Pending (other) Support as well as the Common Form for Biographical Sketch[1]:]

a. For PIs and other senior/key personnel (in both prime and subcontractors, including consultants), please list:

i. Other organizational affiliations and employment

[2] Other Support: https://www.nsf.gov/bfa/dias/policy/researchprotection/commonform_cps.pdf; Biographical Sketch: https://www.nsf.gov/bfa/dias/policy/researchprotection/commonform_biographicalsketch.pdf

ii. Other positions and appointments[2]

iii. Participation in any foreign government-sponsored talent recruitment program(s)[3]

iv. Current and pending support/Other support. For researchers, "Other Support" includes all resources made available to a researcher in support of and/or related to all of their professional R&D efforts, including resources provided directly to the individual rather than through the research organization, and regardless of whether or not they have monetary value (e.g., even if the support received is only in-kind, such as office/laboratory space, equipment, supplies, or employees).] This support includes:

1. all resources made available, or expected to be made available, to an individual in support of the individual's R&D efforts, regardless of (i) whether the source is foreign or domestic; (ii) whether the resource is made available through the entity applying for a research and development award or directly to the individual; or (iii) whether the resource has monetary value;

2. in-kind contributions requiring a commitment of time and directly supporting the individual's R&D efforts, such as the provision of office or laboratory space, equipment, supplies, employees, or students. This includes resource and/or financial support from all foreign and domestic entities, including but not limited to, (i) gifts provided with terms or conditions, (ii) financial support for laboratory personnel, and (iii) participation of student and visiting researchers supported by other sources of funding; and

3. Private equity, venture, or other capital financing.

b. For consultants, please additionally list the following (Note: current, pending, and other support not required):

i. Other organizational affiliations and employment

ii. Other positions and appointments**Error! Bookmark not defined.**

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[2] Both foreign and domestic, including affiliations with foreign entities and governments. This includes titled academic, professional, or institutional appointments whether or not remuneration is received, and whether full-time, part-time, or voluntary (including adjunct, visiting, or honorary).

[3] The term "foreign government-sponsored talent recruitment program" or "foreign government-sponsored talent recruitment programs" means an effort directly or indirectly organized, managed, or funded by a foreign government or institution to recruit S&T professionals or students (regardless of citizenship or national origin, and whether having a full-time or part-time position). Compensation could take many forms including cash, research funding, complimentary foreign travel, honorific titles, career advancement opportunities, promised future compensation, or other types of remuneration or consideration, including in-kind compensation.

iii. Participation in any foreign government-sponsored talent recruitment program(s)

D. Novelty of Proposed Work

Has the proposed work been submitted to any other Government solicitation?

☐ No ☐ Yes

If yes, provide the following information:

- Solicitation number _____
- Agency/Office _____
- Proposed work has already received funding or a positive funding decision.

  ☐ No ☐ Yes ☐ Decision pending

E. Intellectual Property (IP)

[Provide the following information, as applicable.
The IP table in this section should match the table provided with the Commercialization Plan in Volume II and should include any background IP as well as intended IP related to deliverables under the intended OT. The table should be completed appropriately for each type (e.g., background/foreground). Additionally, the Government will assume delivery of Data related to each patent based on the license rights asserted. Thus, data in the table below is intended to relate to items not associated with a patent]

IP Category (Trade Secret, Patent, or Data)	USPTO# and Docket # and Application #	IP Title	Summary of Intended Use in Project	Asserted rights for Government related to FRONT Program (Government Purpose, Unlimited, Limited.)	Name of Person or Entity Asserting Restrictions (wh o owns the IP?)	Funding Source (Federal Government, other, or Mix**)

a. Technical Data and Computer Software

Are you asserting any IP restrictions on any technical data or computer software that will be delivered to the Government?

☐ No ☐ Yes

[If yes, in the table above list all anticipated proprietary claims to results, prototypes, deliverables, or systems supporting and/or necessary for the use of the proposed research, results, prototypes and/or deliverables.

Provide a short summary for each item asserted with less than unlimited rights that describes the nature of the restriction and the intended use of the intellectual property in the conduct of the proposed research. Use the following format for these lists.]

b. Patents

Does the proposed effort involve using patented inventions that are owned by or assigned to the proposing organization or individual?

☐ No ☐ Yes

[If yes, in addition to completing the above table, provide documentation proving ownership or possession of appropriate licensing rights to all patented inventions to be used for the proposed project. If a patent application has been filed for an invention, but it includes proprietary information and is not publicly available, provide documentation that includes: the patent number, inventor name(s), assignee names (if any), filing date, filing date of any related provisional application, and summary of the patent title, with either: (1) a representation of invention ownership; or (2) proof of possession of appropriate licensing rights in the invention (i.e., an agreement from the owner of the patent granting license to the proposer).]

c. Ability to meet programmatic goals with IP/Patent implications

[Describe how IP assertions and/or patent implications impact the applicable ARPA-H programmatic goals.]

F. Human Subjects Research

Does the proposed work involve Human Subjects Research?

☐ No ☐ Yes

[If yes, provide the Federal Wide Assurance (FWA) number and the plan for Institutional Review Board (IRB) review and approval.]

G. Animal Subjects Research

Does the proposed work involve Animal Subjects Research?

☐ No ☐ Yes

[If yes, provide the Animal Welfare Assurance (AWA) number, the Vertebrate Animals Section (VAS), and the plan for Institutional Animal Care and Use Committee (IACUC) review and approval.]

H. Representations Regarding Unpaid Delinquent Tax Liability or a Felony Conviction under Any Federal Law

[Complete the following statements.]

The Proposer represents that –

a. It is ☐ is not ☐ a corporation that has any unpaid Federal tax liability that has been assessed, for which all judicial and administrative remedies have been exhausted or have lapsed, and that is not being paid in a timely manner pursuant to an agreement with the authority responsible for collecting the tax liability,

b. It is ☐ is not ☐ a corporation that was convicted of a felony criminal violation under a federal law within the preceding 24 months.

10 APPENDIX C: TARGET PRODUCT PROFILE GUIDELINES

The Target Product Profiles (TPP) located below provides guidance on the acceptable product specifications for products created by the FRONT program.

FRONT: Target Product Profile (TPP) Guidelines

Proposers must submit a TPP for each disease indication selected, detailing the technologies capabilities. The template below outlines FRONT's minimum expectations but should be expanded and tailored to fit the specific disease indications selected.

Product Properties	Attributes (Ideal)
Indication for Use	Neocortical brain damage due to disease and/or injuries
Target Population	Patients with permanent deficit in cognitive functions e.g. motor or visual
Safety	Meets FDA standards for cell and device therapeutics
Graft Efficacy In Vivo	Restores cognitive function based on parameters such as demonstration of >70% behavioral recovery that is dependent on graft-derived neurons in non-human primate disease models.
Graft Structure	Grafted precursor tissue anastomosis with host and matures with a cytoarchitecture and properties that match natural neocortical tissue.
Graft Stability	Reproducible graft survival (>90%), vascularization within 48 hours, and neural integration within 30% of natural tissue
Intervention	Neocortical precursor tissue transplantation
Administration Route	Surgical implantation
Adverse Events (AEs)	Mild, transient AE may be observed post implantation
Human iPSC Master Bank	GMP compliant human iPSC master bank with shelf life = >10 years at -190 °C, cell viability = >95%
Graft Storage	Viability for >5 days at near freezing or subfreezing temperatures
Clinical Readiness	Product ready for the first in human clinical trial
Product Cost	Initially <$500,000/treatment, with costs dropping to ~$150,000/treatment with scaling and automation

Accessibility	Cost and accessibility to care for all geographical locations within the US by developing solutions with these factors in mind from the start

Steps Required:

1. Define the *healthy or therapeutic range* of select neocortical functions in their indication and propose to restore function to that target range.

2. Include additional *minimal and ideal results* specific to the claim and indication of use for the targeted disease. *Listed examples are not requirements or formal suggestions.*