Broad Agency Announcement (BAA)
Novel Innovations for Tissue Regeneration in Osteoarthritis (NITRO)
Health Science Futures (HSF) Office
75N99223R0003
May 18, 2023

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PART I: OVERVIEW INFORMATION

- **Federal Agency Name –** Advanced Research Projects Agency for Health (ARPA-H), Health Science Futures Office (HSF)
- **Funding Opportunity Title – Novel Innovations for Tissue Regeneration in Osteoarthritis** (NITRO)
- **North American Industry Classification System (NAICS) Codes –** 541714 *Research and Development in Biotechnology (except Nanobiotechnology)* and 541713 *Research and Development in Nanotechnology*
- **Announcement Type –** Initial Announcement
- **Funding Opportunity Number –** 75N99223R0003
- **Assistance Listing Number –** 93.384
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    - Posting Date: **May 18, 2023**
    - Proposers' Day: **June 15, 2023**
        - Proposers' Day Registration Deadline: **June 8, 2023, 12:00 PM EDT**
    - Abstract Due Date and time: **June 23, 2023, 5:00 PM EDT**
    - Proposal Due Date and Time: **July 28, 2023, 5:00 PM EDT**
- **Concise description of the funding opportunity –** The NITRO program vision is to make joints heal themselves. To achieve that goal, the Program aims to develop novel techniques for the regeneration and reconstruction of intra-articular (IA) cartilage and subchondral (SC) bone, the two key tissue types in a joint, in osteoarthritis (OA) patients. The current standard of care for OA patients of all Grades invariably proceeds from physiotherapy and non-steroidal anti-inflammatory (NSAIDs) drugs to open-joint surgery and/or total joint replacement. For patients with Grades I-IV OA, NITRO aims to revolutionize the care algorithm by reversing IA bone and cartilage damage in all synovial joints through infrequent, needle-based and/or non-invasive, long-lasting, approaches in a manner accessible to all Americans. For patients with no IA tissues left to regenerate who have no treatment option other than a total joint replacement, NITRO aims to generate non-immunogenic, load bearing, resorbable, osteochondral joints that require no permanent hardware to be placed inside a patient's body. These technologies will revolutionize the treatment and management of patients with osteoarthritis and drastically decrease the disease burden on patients, providers, and the economy.
- **Anticipated individual awards –** Multiple awards are anticipated.
- **Potential award instruments –** Cooperative Agreements or Other Transaction Agreements (OTA).
- **Agency Contact –** All inquiries shall be sent to NITRO@ARPA-H.gov

PART II: FULL TEXT OF ANNOUNCEMENT

1. Funding Opportunity Description

This publication constitutes a Broad Agency Announcement (BAA) as contemplated in Federal Acquisition Regulation (FAR) 35.016 and 2 Code of Federal Regulations (CFR) § 200.203, and is in accordance with section 499A of the Public Health Service Act. ARPA-H posts this funding opportunity within the framework of a BAA because of its widely recognized use in funding basic and applied research as well as the ability to negotiate multiple award types. 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 proposals to advance regenerative and reconstructive strategies for treating osteoarthritis (OA), using innovative approaches to enable revolutionary advances in patient care algorithms.

Specifically excluded are: 1) proposals that represent an evolutionary or incremental advance in the current state of the art (e.g., advanced titanium or ceramic implants, therapeutics achieving only small repair areas, therapeutics that only slow OA progression without demonstrating regeneration), 2) performers unable to address the objectives of the program, 3) proposals directed towards policy changes, traditional education and training, or center coordination and construction of physical infrastructure are outside the scope of the ARPA-H mission.

1.1. PROGRAM OVERVIEW

Osteoarthritis (OA) is a crippling burden that currently affects 32.5 million US adults and 242 million adults worldwide. OA is often subcategorized into Primary OA (degeneration without a known cause) and Secondary OA. Secondary OA is degeneration with a known cause. The most common causes of Secondary OA are trauma, obesity, and surgery. Secondary OA can also be caused by infection, chemotherapy (particularly paclitaxel and aromatase inhibitors), inflammation, and a range of comorbidities.

By 2040, it is estimated that 26% of the population over 18 (approximately 78.4 million people) will develop some form of arthritis, the most common of which is OA. The number of Americans over the age of 65 will nearly double by 2060, and 88% of the OA population is over the age of 45 so it is anticipated that OA prevalence will increase over time. OA is twice as common in women and has the highest prevalence in Multi-Race Non-Hispanic and Native American/Native Alaskan populations. Additionally, OA rarely occurs as a stand-alone disease, as it is associated with or precipitates other common comorbidities (e.g., increases the risk of heart disease by 50%). Given 50% of the US population is expected to be obese by 2030, there will be a corresponding

surge in cases of Secondary OA. Overall, the disease carries an economic burden of over $136 billion dollars, a portion of which results from opioid-based OA pain management.

Despite the vast health and economic impacts of OA, there are currently no therapeutics to reverse the IA damage caused by the disease. Many patients' first interface with a physician is at the onset of pain, which often means their OA has already significantly advanced in the joint(s). At this point, providers often prescribe NSAIDs (sometimes with corresponding opiates and/or steroids depending on the stage of OA) and recommend physiotherapy to stave off the eventual surgical intervention. Even in cases of activity-related trauma or obesity, there is very little that can be done outside of the aforementioned interventions to slow or reverse OA progression. Once the IA SC bone and cartilage have degenerated the ultimate course of action is an open-joint surgery, typically with a titanium-alloy total joint replacement.

It is currently estimated that there are over 2.5 million joint replacements annually. That number is projected to increase dramatically given the factors described above, and largely due to OA as well as a lack of regenerative therapeutics. While the majority of patients have IA tissues that can be regenerated back to a Grade 0 (Native) status, there are some patients who have no remaining tissue to regenerate and will require a total joint replacement. To successfully address and treat both patient populations, NITRO seeks to revolutionize this entire care algorithm through a two-pronged approach that focuses on (1) the regeneration of SC bone and IA cartilage with a single-dose therapeutic and (2) the creation of patient-specific regenerative and bioresorbable total knee replacements.

1.2 TECHNICAL APPROACH AND STRUCTURE

1.2.1. Technical Areas (TAs)

The NITRO program will develop technologies to enable needle-based and/or non-invasive regeneration of cartilage and bone as well as the total reconstruction of a synovial joint with load-bearing, non-immunogenic, osteo- and chondro-inductive, bioresorbable replacement joints. To accomplish this, the NITRO Program is focused on three TAs:

- **Technical Area 1 (TA1):** Needle-Based and/or Non-Invasive Subchondral (SC) Bone Regeneration. Development of an IA therapeutic to fully regenerate SC bone in all synovial joint(s) in all cases of primary osteoarthritis as well as trauma- and obesity-induced secondary osteoarthritis. **Proposals for TA1 must also include TA2.**
- **Technical Area 2 (TA2):** Needle-Based and/or Non-Invasive Cartilage Regeneration. Development of therapeutics (both IA and systemic) to fully regenerate cartilage in all synovial joints in all cases of primary osteoarthritis as well as trauma- and obesity-induced secondary osteoarthritis. **Proposals for TA2 must also include TA1.**
- **Technical Area 3 (TA3):** Allogeneic and Autogenous Non-Immunogenic, Load-Bearing and Osteochondroinductive Total Replacement Joints. Development of autogenous and allogeneic, non-immunogenic, osteo- and chondro-inductive, load-bearing total knee replacements that requires no permanent foreign body implantation (e.g., is fully bioresorbable, no permanent fixation) and performs at or above the current standard set

for artificial total knee implants. **Proposals for TA3 may be submitted alone or with inclusion of both TA1 and TA2.**

Proposal details: Performers will have the option of submitting proposals that cover TAs in one of the following permutations:

Option A) TA1 and TA2 -or-
Option B) TA3 -or-
Option C) TA1, TA2, and TA3

Proposals for Options A and C that fail to address all the technical areas required as noted above will be deemed non-conforming and may be rejected without further review.

TA1: Needle-Based and/or Non-Invasive Subchondral (SC) Bone Regeneration

Synovial joints are a meeting of two elegantly complex tissues – SC bone and articular cartilage. As OA progresses from mild to moderate to severe, there is progressive damage not just to the articular cartilage but also to the SC bone. Over the course of the disease, this SC (and trabecular) bone ultimately becomes thickened as the condylar head deforms, along with narrowing or obliteration of the joint space and the appearance of cystic bone lesions. While there are a litany of grading scales depending on provider preference and the synovial joint in question, the fact remains that all scales illustrate the progression from a "None" categorization (e.g., "Grade 0" or native with no signs of osteoarthritis) to a "Severe" or End-Grade categorization.

Further complicating the presentation of the disease is the overlying and subjective pain component. Most patients do not present to their healthcare provider until they are at a Minimal-to-Moderate stage when the pain becomes noticeable and/or unbearable. As a result, the almost invariable clinical and surgical algorithm at this point progresses from physiotherapy, NSAIDS (with or without opiates and steroids), and arthroscopy to total joint reconstruction. A purely reconstructive approach to rectify form and function may or may not address the presenting complaint of pain.

Currently, there are no therapeutics that regenerate SC bone or restore the critical structure-function tissue relationships in a joint. Additionally, the cartilage repair therapeutics on the market fail to regenerate subchondral bone and require a two-stage approach (harvest of tissue, followed by expansion then implantation). Further complicating the path towards innovation is the lack of consensus on an ideal *in vitro* (e.g., organoid or joint-on-a-chip) or OA large animal model that can be used for optimized therapeutic discovery and pre-clinical testing for SC bone and cartilage regeneration.

TA1 seeks to create a needle-based and/or non-invasive, single-stage therapeutic that regenerates SC bone and restores the original structure-function relationship within and between SC bone and cartilage. This therapeutic will be administered in a site-specific IA treatment for both single-joint (SJ) and multi-joint (MJ) OA resulting from degeneration, trauma and/or obesity. As a single-stage, one-time, needle-based (to include an arthroscopic approach) and/or non-invasive therapy, TA1 seeks to regenerate SC bone in all cases of OA back to Grade 0 while also providing targeted

pain relief to <3/10 (on the Visual Analogue Scale (VAS)) for all patients. Additionally, the therapeutic must work in tandem with the TA2 therapeutic.

The vision is that a provider can make the clinical decision to regenerate either SC bone (TA1) or cartilage (TA2) or both together as an IA delivery. Thus, both TA1 and TA2 should be able to be administered IA separately or together at a provider's discretion.

The novel SC bone regenerative therapeutic must meet the following specifications:

- ≥1 Needle-based (to include arthroscopic) and/or non-invasive therapeutic(s)
- Therapeutic must work in tandem with TA2
- Be suitable for IA delivery to any synovial joint
- Regeneration of SC bone in all OA stages back to Grade 0 in all synovial joints
- No surgical donor/recipient harvest
- Annual dosing frequency: As infrequently as possible but ideally ≤1/year
- Post-therapeutic pain range: <3/10 VAS
- Patients' return to full function timeline: ≤3mo. post-operation with ≥85% success (failure rate ≤15%)
- Regenerated bone load criteria: Must sustain physiologically relevant load defined by International Classification for Standards (ICS) (e.g., ISO 14243 and 14242) and compared to unaffected, contralateral joint SC bone
- Defect regeneration size: ≥ critical size defect (defined in the metric tables below)
- Must meet all IND Pre-Clinical Safety requirements
- Complete IND application

To achieve the goals of the program, performers may propose a variety of technical approaches to regenerate SC bone. These approaches can be separate or combined (e.g., cell therapy alone or in combination with biomaterials). These may include but are not limited to:

- Implantable scaffolds
- Genetic engineering
- Cell therapy
- Nanoparticles
- Small molecules
- Injectable biomaterials or biologics

Proposers must provide the following information in the proposal:

- Establish therapeutic discovery plan intended for the IA SC bone regenerative for SJ and MJ applications
    - Approach for therapeutic discovery, including but not limited to high-throughput screening, sequencing, or assay development
- Intended *in vitro* assays and/or small animal models to demonstrate efficacy
- Production methods and timeline
- Current manufacturing methods
- Proposed mechanism of action
- Anticipated roadblocks and hurdles with proposed therapeutic approach
- Immunogenicity of proposed therapeutic

- Required ability to combine with and not hinder therapeutic effect of TA2 for a single OA reversal therapy

TA1 metrics (Section 1.3) will increase in difficulty and complexity over the course of the NITRO program. Monthly technical and financial status reports will be required and discussed at monthly meetings with the ARPA-H Program Manager Team. ARPA-H may request performer data as deemed necessary throughout the program to validate technical progress. The IND application, product pipeline, and clinical trials will serve as the Independent Verification & Validation (IV&V) for analysis. Extramural resources and labs may also serve as IV&V during certain aspects of the program to validate findings and assess safety, performance, and efficacy of therapeutics.

TA2: Needle-Based and/or Non-Invasive Cartilage Regeneration

As described in the prior TA1 section, as OA progresses from mild to moderate to severe, there is progressive damage to the articular cartilage. Cartilage is a complex tissue composed of many hierarchical cell types and structural constituents with multiple functions: to absorb force, prevent joint friction through lubrication, bear weight, and tolerate rapid, load-bearing directional changes. As the cartilage degrades, it is unable to lubricate the joint, critical functions are limited, inflammatory mediators fill the joint space, and, over time, it deteriorates, generating severe cartilaginous defects in tandem with the aforementioned SC bone changes and defects. Further complicating the presentation of the disease is the overlying and subjective pain component that is often the impetus for patients to present to their healthcare provider.

Currently, there are no therapeutics that regenerate (as opposed to repair) cartilaginous defects, particularly those classified as “critical size defects”. Moreover, there are no therapeutics that restore the critical structure-function tissue relationships in a joint. As mentioned previously, the cartilage repair therapeutics on the market require an invasive two-stage approach (harvest of recipient/donor tissue, then expansion, and surgical implantation) and can cause donor/recipient site morbidity. Specifically, no therapies exist that are single-stage (e.g., no recipient harvesting required) and can be injected via either IA (for SJ OA) or intravenous (IV) administration (for MJ OA including non-synovial joints).

TA2 seeks to create a needle-based and/or non-invasive, single-stage therapeutic that regenerates cartilage and restores the original structure-function relationship within cartilage, and between SC bone and cartilage. This therapeutic will be administered through an IA approach for SJ (and, potentially, MJ OA at the provider’s discretion) and an IV approach for MJ OA resulting from degeneration, trauma and/or obesity. As a single-stage, one-time, needle-based (to include an arthroscopic approach) and/or non-invasive therapy, TA2 seeks to regenerate all cases of OA back to Grade 0 while also providing targeted pain relief to <3/10 (on the VAS) for all patients. Additionally, the therapeutic must work in tandem with the TA1 therapeutic.

The vision is that a provider can make the clinical decision to regenerate either SC bone (TA1) or cartilage (TA2) or both together as an IA delivery. Thus, both TA1 and TA2 should be able to be administered IA separately or together at a provider’s discretion.

The novel cartilage regeneration therapeutic must meet the following specifications:

- ≥2 Needle-based (to include arthroscopic) and/or non-invasive therapeutic(s)
    - One therapeutic suitable for IA administration to all synovial joints
    - One therapeutic suitable for IV administration to reach all synovial joints
- Therapeutic for IA administration must work in tandem with TA1
- Regeneration of all OA stages back to Grade 0
- No surgical donor/recipient harvest
- Annual dosing frequency: As infrequently as possible but ideally ≤1/year
- Post operative pain range: <3/10 VAS
- Patients' return to full function timeline: ≤3mo. post-operation with ≥85% success (failure rate ≤15%)
- Regenerated cartilage load criteria: Must sustain physiologically relevant load defined by ICS (e.g., ISO 14243 and 14242) and compared to unaffected, contralateral joint cartilage
- Defect regeneration size: ≥ critical size defect (defined in the metric tables below)
- Must meet all IND Pre-Clinical Safety requirements
- Complete IND application

To achieve the goals of the program, performers may propose a variety of technical approaches to regenerate cartilage. These approaches can be separate or combined (e.g., cell therapy alone or in combination with biomaterials). These may include but are not limited to:

- Chondrospheres
- Therapeutic proteins
- Implantable scaffolds
- Genetic engineering
- Cell therapy
- Nanoparticles
- Small molecules
- Injectable biomaterials or biologics

Proposers must provide the following information in the proposal:

- Establish discovery plan intended for the IV and IA cartilage therapeutics for SJ and MJ applications
    - Approach for therapeutic discovery, including but not limited to high-throughput screening, sequencing, or assay development
- Intended *in vitro* assays and/or small animal models to demonstrate efficacy
- Production methods and timeline
- Current manufacturing methods
- Proposed mechanism of action
- Anticipated roadblocks and hurdles with proposed therapeutic approach
- Immunogenicity of proposed therapeutic
- Required ability to combine with and not hinder therapeutic effect of TA1 for a single OA reversal therapy

TA2 metrics (Section 1.3) will increase in difficulty and complexity over the course of the NITRO program. Monthly technical and financial status reports will be required and discussed at monthly

meetings with the ARPA-H Program Manager Team. ARPA-H may request performer data as deemed necessary throughout the program to validate technical progress. The IND application, product pipeline, and clinical trials will serve as the IV&V for analysis. Extramural resources and labs may also serve as IV&V during certain aspects of the program to validate findings and assess safety, performance, and validate the efficacy of therapeutics.

TA3: Allogeneic and Autogenous Non-Immunogenic, Load-Bearing and Osteochondroinductive Total Replacement Joints

Without successful early intervention described in TA1 and TA2, OA progression leads to unbearable pain and complete loss of joint function that necessitates total joint replacement. The most common joint that undergoes replacement is the knee, which is termed total knee arthroplasty (TKA). To support the complex loading and mechanical demands of these joints, current medical devices for joint reconstruction remove the damaged tissues and are permanent implants that utilize a combination of high-strength metals and ceramics without any regeneration. Unfortunately, these implants only provide short-term (10-15 years) return to function. Additionally, there are numerous complications and limitations associated with the current standards of care, including high infection and hardware failure rates (>25%), limited range of motion, persistent pain, nerve damage, and thrombosis. Future non-immunogenic implants that integrate with the native tissue and restore function as a regenerated 'living replacement' without permanent hardware would substantially extend the implant life and reduce complications.

Currently, however, there are no patient-specific, non-immunogenic, load-bearing, chondro- and osteo-inductive, and fully bioresorbable replacement joints that restore full function in end-stage degenerated joints. Without such a regenerative replacement joint, patients who undergo the current standard of care for total joint replacement cycle through a 10–15-year (or faster) loop when a complication with their TKA implant develops. This causes a substantial economic burden for patients and healthcare systems and vastly limits the number of possible treatments. Additionally, at the end-stage of OA, with significant joint degeneration or trauma, patients are often treatment planned for or emergently require a total joint replacement.

For those patients with no IA tissues left to regenerate who have no treatment option other than a total joint replacement, TA3 aims to generate non-immunogenic, load bearing, bioresorbable, osteochondral, allogeneic and autogenous joints that require no permanent hardware to be placed inside a patient's body. Additionally, these novel allografts and autografts aim to restore joint function in ≤4-6 weeks. In order to achieve these goals, it is expected that performers show replacement stability beyond 12 months post-operation and to establish plans for tracking the replacements' stability for the patients' lifetimes.

From a commercialization standpoint, TA3 seeks to manufacture regenerative and bioresorbable TKA allografts in <24 hours and autografts in <30 days. Overall, TA3 seeks to outperform the current standard of care for TKA via non-immunogenic, load bearing and fully bioresorbable osteochondral grafts for 'plug-and-play' joint replacement without permanent hardware fixation.

The novel joint replacement therapeutic must meet the following specifications:

- 1 patient-specific load-bearing TKA allograft AND 1 patient-specific load-bearing TKA autograft
- Be osteo- and chondro-inductive, non-immunogenic, non-cytotoxic, bioresorbable, and non-tumorigenic
- Require no permanent fixation(s)
- Allograft manufacturing time: custom osteochondral graft in <24 hours
- Autograft manufacturing time: custom osteochondral graft in <30 days
- Patients' return to full function timeline: ≤4-6 weeks post-op with ≥85% success (failure rate ≤15%)
- Stability: sustain physiologically relevant load >12 months post-op and plans to track patients for lifetime
- Both implants meet all IND Pre-Clinical Safety requirements
- Complete IND application

Throughout the program, performers will utilize a variety of manufacturing and regenerative approaches to replace joints. To achieve the goals of the program, performers must generate allografts and autografts, but may propose a variety of technical approaches to fabricate the final therapeutic. These approaches can be separate or combined (e.g., 3D and/or bio-printed constructs alone or in combination with off-the-shelf products). These may include but are not limited to:

- Computerized numerical control (CNC) multiscale milling
- Bioreactors (*in vivo* and/or *in vitro*)
- Genetic engineering
- Off-the-shelf products
- 3D and/or bio-printed constructs
- Anatomical materials
- Multi-functional designs
- Cell therapy

Proposers must provide the following information in the proposal:

- Approach to bioresorbable, non-permanent fixation and integration of osteochondral implant
- Methods to demonstrate *in vitro/in vivo* efficacy
- Current manufacturing time and/or plans to improve manufacturing time
- Production/fabrication approach, manufacturing methods, design plans (such as computer automated designs), and proposed mechanism of action or plans thereafter for bioresorbable fixation methods and osteochondral implant
- Strategy plan for collaborations or companies involved with multiple components of the replacement implants' design, fabrication, and implantation
- Any prior *in vitro* data using that implant (with or without permanent hardware fixation)
- Any prior *in vivo* data using that implant (with or without permanent hardware fixation)
- Intended large animal model, *ex vivo* assays, and *in vitro* assays with rationales
- Anticipated roadblocks and hurdles with proposed implant

- Immunogenicity of proposed implant

TA3 metrics (Section 1.3) will increase in difficulty and complexity over the course of the NITRO program. Monthly technical and financial status reports will be required and discussed at monthly meetings with the ARPA-H Program Manager Team. ARPA-H may request performer data as deemed necessary throughout the program to validate technical progress. The IND application, product pipeline, and clinical trials will serve as the IV&V for analysis. Extramural resources and labs may also serve as IV&V during certain aspects of the program to validate findings and assess safety, performance, and validate the efficacy of therapeutics.

1.2.2. Program Structure

The NITRO program will be accomplished over 2 sequential Phases of increasing technical complexity. NITRO Phases will include programmatic elements to ensure performer success, including check points at each transition between NITRO Phases, active and regular US Government stakeholder engagement, establishment of current Good Manufacturing Practices (cGMP) and Good Laboratory Practice (GLP)-compliant manufacturing, equity for disparate patient and market settings for patient/provider buy-in, and utilization of Project Accelerator Transition Innovation Office (PATIO) assets for commercialization (e.g., Expert/Entrepreneur in Residence (XIR/EIR) meetings).

ARPA-H NITRO OA Model Symposium

To address the lack of a consensus ideal OA large animal model, NITRO has utilized a Special Notice to immediately launch the ARPA-H NITRO OA Model Symposium. To develop the ideal OA Model for therapeutic translation in pre-Clinical studies, the OA Model Symposium includes all interested parties (from academia to industry) wishing to provide input and rationale to help guide the Symposium towards a single, ideal animal model. Importantly, the Symposium will also include US Government Stakeholders (e.g., members of the FDA), veterinarians, contract research organizations (CROs), and manufacturers. It is strongly encouraged that all NITRO performers (both prospective and active) actively participate in the Symposium. It should be noted that many models of OA exist, however, the ideal model is widely disputed. This symposium aims to discuss the data and technology to date to provide consensus surrounding an appropriate model. This Symposium will begin as soon as possible with the aim of generating a consensus ideal large animal model by the start of Q4 of FY25. It is expected that, once a consensus model is established, contributors to the Symposium will publish their findings to streamline the path forward for NITRO performers and the rest of academia/industry. Additionally, NITRO aims to have frequent and robust US Government regulatory input to ensure that the consensus model coincides with the FDA's requirements for Pre-Clinical Data/IND Enabling Studies.

Equity Requirements

ARPA-H has indicated it is committed to equitable healthcare access irrespective of race, ethnicity, gender/gender identity, sexual orientation, disability, geography, employment, insurance, and

socioeconomic status. It is also the goal of the program to negotiate full coverage through all health insurance via US Government entities (Center for Medicare and Medicaid Innovation (CMMI), Centers for Medicare & Medicaid Services (CMS), Indian Health Service (IHS), and more) so that NITRO therapeutics are accessible to all. To that end, NITRO will mandate that each performer accounts for and actively engages with an **Equity Officer (EO)** who will be full-time and dedicated to the project. The EO will ensure that all performers follow the FDA's guidance titled "Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials" and that clinical trial populations reflect the same US population proportions and severity as those affected by OA. The EO will be approved by ARPA-H and will help perform key duties throughout all NITRO Phases, as described below. In NITRO Phase 1, the EO will define Equity Key Performance Indicators (KPIs), establish >5 demographic-specific listening sessions, prepare the "Road Map to Equity" report, create the Insurance Action Plan (with CMMI, CMS, and HHS engagement). In NITRO Phase 2, the EO will co-manage and publish the proceedings of the Equity Symposium, ensure that the prior KPIs are enforced, and implement the Clinical Trial Go/No-go Demographic Requirements, as described below. The EO will develop rollout strategies and triangulate stakeholders with the help of ARPA-H's XIR/EIR network, and the EO will also pursue all available approaches to ensure equity throughout study designs and Clinical Trials across all TA's.

NITRO EO Metrics

The EO will proactively work toward equitable demographic representation throughout and understand the unique barriers to healthcare access for different populations. Further, some populations will be more difficult to reach due to historical disenfranchisement, lack of other Government investments, and distrust of Government programming. Reparative work may be required to bring these Americans to the table, and it is ARPA-H's expectation that performers and the EO will do so. Performers and the EO must seek out and establish mutually respectful relationships with community leaders and pre-existing communities of care as their understanding of community pain points. The selected EO must be approved by ARPA-H.

The duties of the EO in NITRO Phase 1 include:

- Define key performance indicators (KPIs) and metrics of equitable research for all performers and stakeholders to follow during study design and execution
- Listening Sessions Action Plan: Proactively identify risks/challenges of equity in OA basic science and clinical research and convene OA patient listening sessions focused on the impact of OA on their lives, and what might prevent them from accessing NITRO therapeutics, including but not limited to: medical mistrust, comfort with the idea of NITRO therapeutics, willingness-to-pay, likelihood of seeking the treatment, as well as physical, economic, and social barriers to access.
    - ≥5 Listening sessions with follow up reports
        - EO's must conduct sessions with 1) Native American/ Native Alaskans, 2) non-Hispanic Black Americans, and 3) Either Latino or AAPI Americans, with the remaining 2 sessions at the EO's discretion

    - Women must make up >50% of the group recruited for each session
- Prepare the "Road Map to Equity" report to deliver at the Equity Symposium
    - Liaise with patient advocacy groups, insurance representatives and with the Department of Health and Human Services Office of Minority Health
    - Deliver the final report on the listening sessions including barriers unique to each patient population and the identified strategies to overcome those barriers
- Insurance Action Plan: Coordinate with ARPA-H and Insurance Stakeholders to streamline NITRO therapeutics into the standard of care at ≤25% of the current cost of OA treatments

ARPA-H NITRO OA Equity Symposium

EO officers from all performer teams will liaise with ARPA-H to plan and execute the Equity Symposium at the end of NITRO Phase 1. EO's will present their Road Map to Equity that will include a detailed executive summary of the team's KPIs, listening sessions, community assessments, Insurance Action Plan, as well as a specific execution plan with timelines and milestones to completion. The Road Map to Equity must include an equity recruitment plan to reach enrollment of >50% women and enrollment (±5%) of 21% Multi-Racial Non-Hispanic (Multi-NH); 20% Native American/Native Alaskan (Native Am/AK); 18% Non-Hispanic White (NHW); 18% Non-Hispanic Black (NHB); 13% Latino (LAT); 10% Asian American Pacific Islander (AAPI) as well as robust risk mitigation plans. These Values reflect the demographic distribution of arthritis in the US and serve as an accurate demonstration of the correlation between race and OA in the US.

The duties of the EO in NITRO Phase 2 include:

- Co-manage the ARPA-H NITRO Equity Symposium and publish the proceedings
- Ensure that prior KPIs from NITRO Phase 1 duties are enforced
- Implement and de-risk Clinical Trial Go/No-Go Demographic Requirements:
    - Enrollment of >50% women and
    - Enrollment (±5%) of 20.7% Multi-NH; 20.1% Native Am/AK; 18.6% NHW; 18.2% NHB; 12.7% LAT; 9.7% AAPI (normalized and based on data from the Center for Disease Control and Prevention (CDC) statistics on disparities and age-adjusted prevalence of doctor-diagnosed arthritis and arthritis-attributable activity limitations)

NITRO Go/No-Go Phase 2 Checkpoint

At the 12-month mark in NITRO Phase 2 (end of Q4 in FY26), there will be a Go/No-Go determination based on performance against NITRO Phase 2.1 metrics in the OA Large Animal Model, as described below in the metrics tables. A "No-Go" determination means that performers will not proceed into the remaining program option periods and will no longer be NITRO performers. A "Go" determination means that performers will be able to proceed into the remaining program option periods. Performers will qualify for the "No-Go" determination in TA1 and TA2 if at 12 months they have not performed satisfactorily against Phase 2.1 requirements in

the OA Large Animal Model and/or have failed components of their IND-enabling studies to date. Performers that do meet these requirements will qualify for the "Go" determination. Performers will qualify for the "No-Go" determination in TA3 if at 12 months they have not performed satisfactorily against Phase 2.1 requirements and/or have failed components of their IND-enabling studies to date. Performers that do meet these requirements will qualify for the "Go" determination.

Additionally, any performer across all TAs that does not meet the Equity KPIs set by the EO may also be given a "No-Go" determination.

TA1 and TA2:

NITRO Phase 1 (24 Months): Therapeutic Discovery & *In Vitro* Assessment

During the 24-month NITRO Phase 1, performers will identify and produce targeted therapeutics for SC bone and cartilage regeneration in single-joint (SJ) and multi-joint (MJ) OA in all synovial joints. For TA1, performers must produce only an intra-articular (IA) therapeutic. For TA2, performers must produce both an IA therapeutic and a systemic (e.g., IV) therapeutic. See Figure 1 for full program overview.

During NITRO Phase 1, all performers will demonstrate *in vitro* that their intended therapeutic 1) ideally requires at most one annual dosing, 2) subsequently regenerates all stages of OA back to Grade 0, and 3) can feasibly be delivered via a needle (including an arthroscopic approach) or non-invasive method. The vision is that a provider can make the clinical decision to regenerate either SC bone (TA1) or cartilage (TA2) or both together as an IA delivery. Thus, both TA1 and TA2 should be able to be administered IA separately or together at a provider's discretion.

- Goals of NITRO Phase 1 (metrics defined in Section 1.3)
    - Produce a needle-based and/or non-invasively delivered regenerative therapeutic for both IA cartilage and SC bone in all synovial joints
        - For cartilage, performers must also produce a systemic cartilage regenerative for multi-joint OA
        - Ideal target is an IA, needle-based and/or non-invasive therapeutic that is administered no more than once-per-year and regenerates both cartilage and SC bone in all synovial joints with only one surgical procedure and no surgical donor/recipient harvest
    - Regenerate all IA bone and cartilage, regardless of OA stage, to Grade 0
    - Regenerate any critical size (and greater) cartilage defect
    - Begin IND application
    - Identify potential GLP and cGMP manufacturing partners
    - By Q4 FY24: Submit INTERACT meeting package and incorporate feedback
    - By Q3 FY25: Submit Pre-IND meeting package and incorporate feedback
    - Work with PATIO assets to develop commercialization plan (including an engagement plan with XIR/EIRs)

TA1 and TA2:

NITRO Phase 2 (36 Months): Pre-Clinical Trials & Phase I Clinical Trials (each 18 months)

During the 36-month NITRO Phase 2, performers will demonstrate safety, efficacy, and scalability of their TA1 and TA2 therapeutic first in the Consensus OA Large Animal Model and then in Phase I Clinical Trials. See Figure 1 for full program overview.

- Goals of NITRO Phase 2 (metrics defined in Section 1.3)
    - Pre-Clinical (in Appropriate OA Large Animal Model)
        - Having met all criteria of NITRO Phase 1, therapeutics must demonstrate regeneration of SC bone and cartilage in OA Large Animal Model with a go/no-go determination at the end of Q4 in FY26
        - Fulfill the requirements of a pre-IND submission, including:
            - Demonstrate established GLP compliant for all *in vivo* testing
            - Demonstrate established partner and pathway towards producing cGMP material for 20-100 patients
        - Demonstrate pain <3/10 on VAS
        - Demonstrate full return to function in ≤3 months post-op with ≥85% success
        - Demonstrate sustained physiologically-relevant load (consistent with ISO metrics and compared to unaffected, contralateral joint in the same animal)
        - Complete all IND-enabling studies (& submit IND application)
        - Use PATIO Assets to commence commercialization plan, secure IP, streamline regulatory pathway (FDA consultants), scale manufacturing capabilities, etc.
    - Phase I Clinical Trials
        - Having met all criteria of the pre-Clinical phase, therapeutics must continue to meet and/or exceed all prior criteria in Phase I Clinical Trials
        - Demonstrate efficacy and safety in human trials
        - GLP compliant
        - Demonstrate scalable cGMP manufacturing partner for Phase II/II/Commercial applications (1000+ patients)
        - Demonstrate path towards Phase II/III Clinical Trials
        - Use PATIO assets to commercialize therapeutics and exit Program

TA3:

NITRO Phase 1 (24 Months): Therapeutic Discovery & *In Vitro* Assessment

During the 24-month NITRO Phase 1, TA3 performers will demonstrate *in vitro* & *in vivo* the efficacy of their implantable devices. All performers must generate: **a patient-specific allograft osteochondral implant and an autograft osteochondral implant**. Both implants must be for total knee arthroplasty (TKA). **None** of the load-bearing implants may use or require any permanent fixation. The ultimate therapeutic goal might be an off-the-shelf or print-on-demand implant 'ghost' that can be populated with autologous or allogeneic cells. See Figure 1 for full program overview.

The expected application of the allograft is for a 'plug-and-play' implant for any patient with significant joint trauma who can only wait up to 24 hours for an osteochondral replacement. The expected application of the autograft is for a patient who can afford (time, health, pain control, etc.) to wait up to 30 days for a bio-resorbable, patient specific, load-bearing, osteochondral replacement that will never require replacement due to implant failure.

Further, by the end of NITRO Phase 2 (Phase I Clinical Trials), the expected turnaround time for the TKA osteochondral allografts is less than 24 hours. The expected turnaround time for the TKA osteochondral autograft is less than 30 days. At a minimum, all implants are expected to sustain mechanical load as defined by the relevant ISO Standards.

- Goals of NITRO Phase 1 (metrics defined in Section 1.3)
    - Produce load-bearing, patient-specific osteochondral allograft for TKA
        - **AND**
    - Produce load-bearing, patient-specific osteochondral autograft for TKA
    - For all implants:
        - Demonstrate that implants are patient-specific, osteo- and chondro-inductive, non-cytotoxic, bioresorbable, and load-bearing
        - Identify potential GLP and cGMP manufacturing partners
        - Begin IND application
        - Demonstrate safety, efficacy, and reproducibility of chosen autogenous harvest location, cell type for expansion, and any genetic modifications that is cGMP- compliant
        - Demonstrate bioreactor design, including post-culture structural and mechanical properties before implantation time, and bioreactor scalability for autogenous implant
        - Demonstrate safety, efficacy, and reproducibility of stem cell line or cell genetic modifications for allograft implant that is both cGMP-compliant
        - By Q4 FY24: Submit INTERACT meeting package and incorporate feedback
        - By Q3 FY25: Submit Pre-IND meeting package and incorporate feedback
        - Work with PATIO assets to develop commercialization plan (including an engagement plan with XIR/EIRs)

NITRO Phase 2 (36 Months): Phase I Clinical Trials

During the 36-month NITRO Phase 2, performers will demonstrate NITRO Phase 1 implants in Phase I Clinical Trials for 20-100 patients. See Figure 1 for full program overview.

- Goals of NITRO Phase 2 (metrics defined in Section 1.3)
    - Pre-Clinical
        - Having met all prior criteria in NITRO Phase 1, implants must continue to meet and/or exceed all prior criteria in pre-Clinical Trials with a go/no-go determination at the 12-month mark

- Demonstrate efficacy, stability, and complete integration at implant site (with no osteophytes, non- or mal-unions), and with only non-permanent fixation
- Demonstrate implants are patient-specific, non-tumorigenic, non-immunogenic
- Demonstrate patient-specific osteochondral TKA allograft can be produced in <24 hours
- Demonstrate patient-specific osteochondral TKA autograft can be produced in <30 days
- Demonstrate all implants sustain physiologically-relevant load (consistent with ISO metrics) and can withstand appropriate stress and strain as compared to unaffected, contralateral joint
- Demonstrate *in vivo* that the animal model can return to function in ≤4-6 weeks post-op ≥85% success
- Demonstrate stability of the implant ≥12 months with ≥85% success
- Complete all IND-enabling studies (& submit IND application)
- GLP compliant
- Produce cGMP material for 20-100 patients
- Use PATIO Assets to commence commercialization plan, secure IP, streamline regulatory pathway (FDA consultants), scale manufacturing capabilities, etc.

o Phase I Clinical Trial

- Having met all prior criteria in NITRO Phase 1, implants must continue to meet and/or exceed all prior criteria in Phase I Clinical Trials
- Demonstrate efficacy and safety in human trials
- Demonstrate established manufacturer of therapeutic with cGMP capacity for Phase II/III/Commercial (1000+ patients)
- Demonstrate path forward towards Phase II/III Trials
- Use PATIO assets to commercialize therapeutics and exit Program

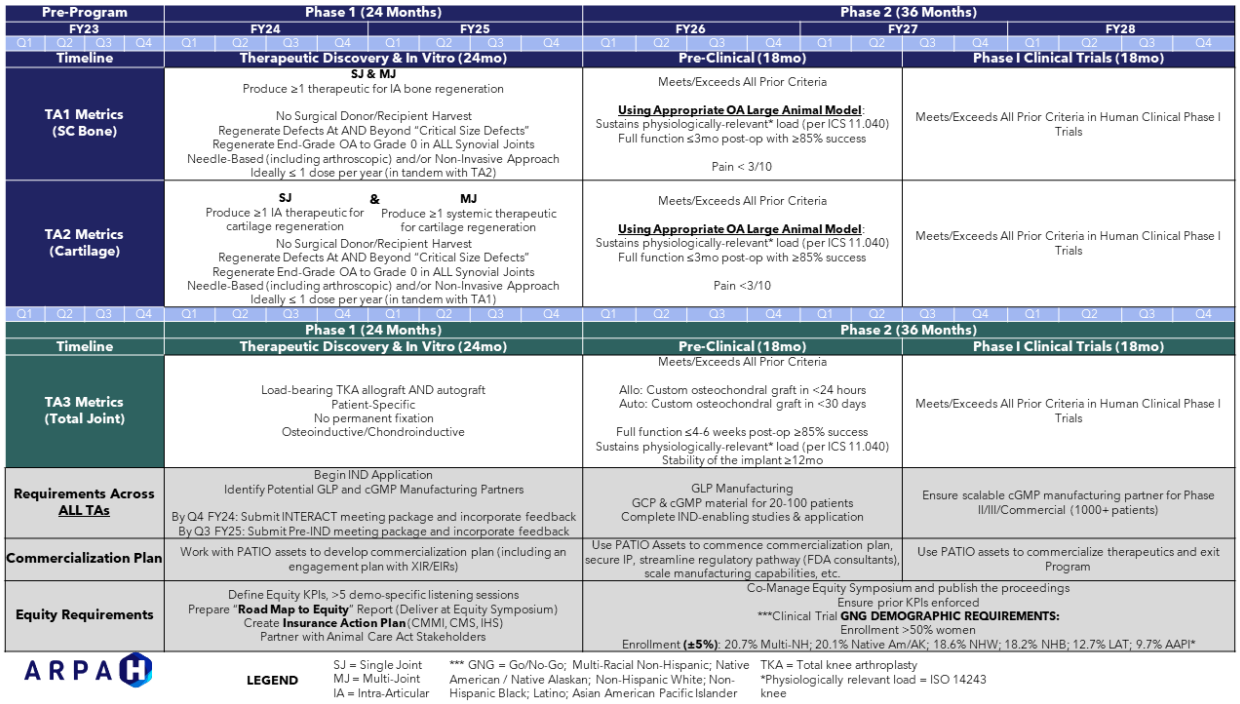

Figure 1. Program Structure and General Overview

1.3 PROGRAM METRICS

To evaluate how effectively a proposed solution will achieve the stated program objectives, the Government hereby promulgates the following program metrics that may serve as the basis for determination of satisfactory progress to warrant continued funding. Although the program metrics are specified below, proposers should note that the Government has identified these goals with the intention of bounding the scope of effort while affording maximum flexibility, creativity, and innovation of proposed solutions to the stated problem. Proposals should cite the quantitative and qualitative success criteria that the effort will achieve by each Phase's program milestone and intermediary metric measurement.

TA1 Metrics and Objectives

The overall program goals for TA1 are listed in Table 1. The expected metrics per phase in TA1 are listed in Table 2. In addition to frequent performance reviews throughout the phases, performers must provide an **end-of-phase final report** that summarizes all efforts and data for each completed NITRO Phase.

Table 1. TA1 Overall Program Goals

# Of Therapeutics	≥1
Therapeutic Requirements	Single-joint (SJ) & multi-joint (MJ) treatment. **Therapeutic must work in tandem with TA2**
Delivery Location(s)	Intra-articular (IA)
Required Therapeutic Activity	SC bone regeneration*; (Regeneration of all OA stages back to Grade 0) including critical size defects^{+}

Post-Op Pain Goal	<3/10 on Visual Analog Scale (VAS)
Therapeutic Delivery	Needle-based (to include arthroscopic) and/or non-invasive
Dose Frequency	As infrequently as possible but ideally ≤1/year
# Of Surgical Procedures	One (No surgical donor/recipient harvest)
Therapy Success Rate	≥85% with full joint function ≤3 months post-op
Functional Requirement	Weight bearing/load capacity ≈ contralateral joint
Manufacturing Goal(s)	≥ 1000 patients (established cGMP manufacturing partner to scale)
Clinical Trials Goals	Complete IND-enabling studies & Phase I Clinical Trials
Equity Requirements	Insurance Action Plan, 'Road Map to Equity' report, Equity Symposium management, Clinical Trial Equity per Go/No-Go Demographics Requirements

*SC bone regeneration may include but is not limited to restoration of trabecular space without cysts, restored tidemark and without pathogenic thickening of the SC plate. This must work in tandem with TA2 therapeutic(s), below.

+Critical size defects: those that would not spontaneously heal completely and without therapeutic intervention

Table 2. TA1 Metrics for Each Phase and Sub-Phase

Metrics	**Specifications**
Program Q1-Q8	*Phase 1 (Discovery & In Vitro)*
Therapeutic Approach	Needle-Based (to include arthroscopic) and/or Non-Invasive regenerative
# Of Therapeutics	≥1 (for IA administration for SJ & MJ)
Regeneration Target	Regeneration of all OA stages back to Grade 0 (Native) and for any subchondral defect, to include those beyond a "critical size defect", *in vitro* and/or in small animal models
Dosing Frequency	As infrequently as possible but ideally ≤1/year
# Of Surgical Procedures	One (No surgical donor/recipient harvest)
Equity Requirements	1) Define Equity KPIs, >5 demo-specific listening sessions 2) Prepare "Road Map to Equity" Report (Deliver at Equity Symposium) 3) Create Insurance Action Plan (CMMI, CMS, IHS)
Additional Requirement(s):	1) Therapeutic must work in tandem with TA2 2) Work with PATIO assets to develop commercialization plan (including an engagement plan with XIR/EIRs) 3) By Q4 FY24: Submit INTERACT meeting package and incorporate feedback 4) By Q3 FY25: Submit Pre-IND meeting package and incorporate feedback 5) Begin IND Application 6) Identify potential GLP and cGMP Manufacturing Partners
Program Q9-Q14	*Phase 2.1 (Pre-Clinical)*
Must Continue to Meet/Exceed ALL Prior Criteria in Pre-Clinical Trials	
Post-Op Pain Goal	<3/10 on VAS
Full Function Timeline	Full joint function in ≤3 months with ≥85% success
Regenerated SC Bone Mechanical Properties	Sustained, physiologically relevant load defined by International Classification for Standards (ICS) (e.g., ISO 14243 and 14242) and compared to unaffected, contralateral joint SC bone
Safety Threshold	Complete all IND-enabling studies (& submit IND application) with a go/no-go determination at the 12-month mark
Manufacturing Standards	1) GLP compliant 2) Produce cGMP material for 20-100 patients

Equity Requirements	1) Co-Manage Equity Symposium and publish the proceedings 2) Ensure prior KPIs enforced
Additional Requirement(s):	Use PATIO Assets to commence commercialization plan, secure IP, streamline regulatory pathway (FDA consultants), scale manufacturing capabilities, etc.
Program Q9-Q14	*Phase 2.2 (Phase I Clinical Trial)*
Must Continue to Meet/Exceed ALL Prior Criteria in Human Clinical Phase I Trials	
Manufacturing Standards	1) GLP compliant 2) Ensure scalable cGMP partner for Phase II/III/Commercial (1000+ patients)
Equity Requirements	1) Ensure prior KPIs enforced 2) Clinical Trial GNG DEMOGRAPHIC REQUIREMENTS a) Enrollment >50% women b) Enrollment (±5%) of 20.7% Multi-NH; 20.1% Native Am/AK; 18.6% NHW; 18.2% NHB; 12.7% LAT; 9.7% AAPI*
Additional Requirement(s):	Use PATIO assets to commercialize therapeutics and exit Program

*GNG = Go/No-Go; Native American / Native Alaskan; Non-Hispanic Multi-Racial; Non-Hispanic Black, Non-Hispanic White; Latino; Asian American Pacific Islander. These GNG Values are normalized and based on data from CDC statistics on disparities and age-adjusted prevalence of doctor-diagnosed arthritis and arthritis-attributable activity limitations.

TA2 Metrics and Objectives

The overall program goals for TA2 are listed in Table 3. The expected metrics per phase in TA1 are listed in Table 4.

Table 3. TA2 Overall Program Goals

# Of Therapeutics	≥2
Therapeutic Requirements	SJ & MJ treatment. **Therapeutic must work in tandem with TA1.**
Delivery Location(s)	IA for SJ, IV for MJ
Required Therapeutic Activity	Cartilage regeneration* (Regeneration of all OA stages back to Grade 0) including critical size defects+
Post-Op Pain Goal	<3/10 on VAS
Therapeutic Delivery	Needle-based (to include arthroscopic) and/or non-invasive
Dose Frequency	As infrequently as possible but ideally ≤1/year
# Of Procedures	One (No surgical donor/recipient harvest)
Therapy Success Rate	≥85% with full joint function ≤3 months post-op
Functional Requirement	Weight bearing/load capacity ≈ contralateral joint
Manufacturing Goal(s)	≥ 1000 patients (established cGMP manufacturing partnership to scale)
Clinical Trials Goals	Complete IND-enabling studies & Phase I Clinical Trials
Equity Requirements	Insurance Action Plan, 'Road Map to Equity' report, Equity Symposium management, Clinical Trial Equity per Go/No-Go Demographics Requirements

*Cartilage regeneration may include but is not limited to restoration of hierarchical structures, joint lubrication, and tidemark without pathogenic erosion, fissures, or loss of proteoglycan. This must work in tandem with TA1, above.
+Critical size defects: those that would not spontaneously heal completely and without therapeutic intervention

Table 4. TA2 Metrics for Each Phase and Sub-Phase

Metrics	Specifications
Program Q1-Q8	*Phase 1 (Therapeutic Discovery & In Vitro)*
Therapeutic Approach	Needle-Based (to include arthroscopic) and/or Non-Invasive regenerative
# Of Therapeutics	≥2 (1 for IA SJ, 1 for systemic MJ administration)
Regeneration Target	Regeneration of all OA stages back to Grade 0 (Native) and for any cartilage defect, to include those beyond a "critical size defect", *in vitro* and/or in small animal models
Dose Frequency	As infrequently as possible but ideally ≤1/year
# Of Surgical Procedures	One (No surgical donor/recipient harvest)
Equity Requirements	1) Define Equity KPIs, >5 demo-specific listening sessions 2) Prepare "Road Map to Equity" Report (Deliver at Equity Symposium) 3) Create Insurance Action Plan (CMMI, CMS, IHS)
Additional Requirement(s):	1) Therapeutic must work in tandem with TA2 2) Work with PATIO assets to develop commercialization plan (including an engagement plan with XIR/EIRs) 3) By Q4 FY24: Submit INTERACT meeting package and incorporate feedback 4) By Q3 FY25: Submit Pre-IND meeting package and incorporate feedback 5) Begin IND Application 6) Identify potential GLP and cGMP Manufacturing Partners
Program Q9-Q14	*Phase 2.1 (Pre-Clinical)*
Must Continue to Meet/Exceed ALL Prior Criteria in Pre-Clinical Trials	
Post-Op Pain Goal	<3/10 on VAS
Full Function Timeline	Full joint function in ≤3 months with ≥85% success
Regenerated Cartilage Mechanical Properties	Sustained, physiologically-relevant load defined by ICS (e.g., ISO 14243 and 14242) and compared to unaffected, contralateral joint cartilage
Safety Threshold	Complete all IND-enabling studies (& submit IND application) with a go/no-go determination at the 12-month mark
Manufacturing Standards	1) GLP compliant 2) Produce cGMP material for 20-100 patients
Additional Requirement(s):	Use PATIO Assets to commence commercialization plan, secure IP, streamline regulatory pathway (FDA consultants), scale manufacturing capabilities, etc.
Program Q15-Q20	*Phase 2.2 (Phase I Clinical Trial)*
Must Continue to Meet/Exceed ALL Prior Criteria in Human Clinical Phase I Trials	
Manufacturing Standards	1) GLP compliant 2) Ensure scalable cGMP partner for Phase II/III/Commercial (1000+ patients)
Equity Requirements	1) Ensure prior KPIs enforced 2) Clinical Trial GNG DEMOGRAPHIC REQUIREMENTS a) Enrollment >50% women b) Enrollment (±5%) of 20.7% Multi-NH; 20.1% Native Am/AK; 18.6% NHW; 18.2% NHB; 12.7% LAT; 9.7% AAPI*
Additional Requirement(s):	Use PATIO assets to commercialize therapeutics and exit Program

*GNG = Go/No-Go; Native American / Native Alaskan; Non-Hispanic Multi-Racial; Non-Hispanic Black, Non-Hispanic White; Latino; Asian American Pacific Islander. These GNG Values are normalized and based on data from CDC statistics on disparities and age-adjusted prevalence of doctor-diagnosed arthritis and arthritis-attributable activity limitations.

TA3 Metrics and Objectives

The overall program goals for TA3 are listed in Table 5. The expected metrics per phase in TA3 are listed in Table 6.

Table 5. TA3 Overall Program Goals

# Of Implants	2 (1 allograft and 1 autograft)
Implant Requirements	Patient-specific, non-immunogenic, osteo- and chondro-inductive, load-bearing, and bioresorbable replacement joints with stable integration and without permanent fixation
Delivery Location(s)	Knee
# Of Surgical Procedures	1 (for allograft), ≤2 (for autograft)
Implant Success Rate	≥85% with full function ≤4-6 weeks post-op & stability for ≥12 months post-op
Functional Requirement	Weight bearing/load capacity ≈ contralateral joint
Manufacturing Goal(s)	≥1000 patients (established cGMP manufacturing partnership to scale)
Clinical Trials Goals	Complete IND-enabling studies & Phase I Clinical Trials
Equity Requirements	Insurance Action Plan, 'Road Map to Equity' report, Equity Symposium management, Clinical Trial Equity per Go/No-Go Demographics Requirements

Table 6. TA3 Metrics for Each Phase and Sub-Phase

Metrics	**Specifications**
Program Q1-Q8	*Phase 1 (Therapeutic Discovery & In Vitro)*
Implant Approach	Allograft and autograft for load-bearing total knee arthroplasty (TKA)
# Of Implants	2 (1 allograft and 1 autograft)
Manufacturing Timeline	Allograft: <24 hours, Autograft: <30 days
***In Vitro* Implant Requirements**	Patient-specific, osteo- and chondro-inductive, non-cytotoxic, bioresorbable, and load-bearing
Equity Requirements	1) Define Equity KPIs, >5 demo-specific listening sessions 2) Prepare "Road Map to Equity" Report (Deliver at Equity Symposium) 3) Create Insurance Action Plan (CMMI, CMS, IHS)
Additional Requirement(s):	1) By Q4 FY24: Submit INTERACT meeting package and incorporate feedback 2) By Q3 FY25: Submit Pre-IND meeting package and incorporate feedback 3) Begin IND Application 4) Identify potential GLP and cGMP Manufacturing Partners 5) Work with PATIO assets to develop a commercialization plan (including an engagement plan with XIR/EIRs)
Program Q9-Q14	*Phase 2.1 (Pre-Clinical)*
Must Continue to Meet/Exceed ALL Prior Criteria in Pre-Clinical Trials	
Full Function Timeline	Full joint function in ≤4-6 weeks with ≥85% success

Stability Timeline	Full joint function and stability for ≥12 months with ≥85% success
***In Vivo* Implant Requirements**	In addition to meeting all *in vitro* requirements, the implants must also now be: patient-specific and non-immunogenic with stable integration and without permanent fixation
Integrated Implant Mechanical Properties	Sustained, physiologically relevant load defined by ICS (e.g., ISO 14243 and 14242) and compared to unaffected, contralateral joint
Safety Threshold	Complete all IND-enabling studies (& submit IND application) with a go/no-go determination at the 12-month mark
Manufacturing Standards	1) GLP compliant 2) Produce cGMP material 20-100 patients
Additional Requirement(s):	Use PATIO Assets to commence commercialization plan, secure IP, streamline regulatory pathway (FDA consultants), scale manufacturing capabilities, etc.
Program Q15-Q20	*Phase 2.2 (Phase I Clinical Trial)*
Must Continue to Meet/Exceed ALL Prior Criteria in Human Clinical Phase I Trials	
Manufacturing Standards	Ensure scalable cGMP partner for Phase II/III/Commercial (1000+ patients)
Equity Requirements	1) Ensure prior KPIs enforced 2) Clinical Trial GNG DEMOGRAPHIC REQUIREMENTS a) Enrollment >50% women b) Enrollment (±5%) of 20.7% Multi-NH; 20.1% Native Am/AK; 18.6% NHW; 18.2% NHB; 12.7% LAT; 9.7% AAPI*
Additional Requirement(s):	Use PATIO assets to commercialize therapeutics and exit Program

*GNG = Go/No-Go; Native American / Native Alaskan; Non-Hispanic Multi-Racial; Non-Hispanic Black, Non-Hispanic White; Latino; Asian American Pacific Islander. These GNG Values are normalized and based on data from CDC statistics on disparities and age-adjusted prevalence of doctor-diagnosed arthritis and arthritis-attributable activity limitations.

1.4 GENERAL REQUIREMENTS

1.4.1. Proposing Teams

It is expected proposals will involve teams with the **expertise needed to achieve the goals** of both TA1 and TA2, TA3 independently, or all 3 TAs collectively. Specific content, communications, networking, and team formation are the sole responsibility of the proposer[1]. Proposers must submit a single, integrated proposal led by a Principal Investigator (PI), under a single prime awardee[2] that addresses all program Phases, as applicable. Proposers may only submit one proposal as the prime proposer.

ARPA-H will hold a Proposers' Day (see Section 8, *Other Information*) to facilitate the formation of proposer teams and enable sharing of information among interested proposers.

[1] Proposer refers to all respondents to this Broad Agency Announcement, regardless of resulting award instrument.

[2] Awardee is synonymous with performer and in this announcement refers to any entity entering into an award with the Government. Prime awardee is thus synonymous with prime performer. Subawardees refer to entities performing in support of a Government award, without a direct award from the Government (i.e., support is provided directly to the prime performer or other tier subawardee).

2. Award Information

2.1 GENERAL AWARD INFORMATION

Multiple awards are anticipated. The resources made available under this BAA, and number of awards made will depend on the quality of the proposals[3] received and the availability of funds. ARPA-H reserves the right to make multiple awards, a single award, or no awards.

The Government reserves the right to select for negotiation all, some, one, or none of the proposals received in response to this BAA and to make awards without negotiations with proposers. The Government also reserves the right to conduct negotiations if it is later determined to be necessary. Additionally, ARPA-H reserves the right to accept proposals in their entirety or to select only portions of proposals for negotiation and award. The Government reserves the right to fund proposals in phases, including as optional phases, as applicable.

Proposals identified for negotiation are expected to result in cooperative agreements and/or OTAs. Selection of award instrument will be based upon consideration of the nature of the work proposed, the required degree of interaction between parties, and other factors. The Government may request additional necessary documentation, tailored to the individual proposals once it makes the award instrument determination. The Government reserves the right to remove proposals from award consideration should the parties fail to reach agreement on award terms, conditions, and/or cost/price within a reasonable time, and/or if the proposer fails to timely provide requested additional information.

Proposers looking for innovative, commercial-like contractual arrangements are encouraged to consider requesting OTAs.

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

3. Eligibility Information

3.1. ELIGIBLE APPLICANTS

All responsible sources capable of satisfying the Government's needs may submit a proposal.

[3] In this document, proposal refers both to the abstract and the full proposal unless otherwise indicated.

3.1.1. Federally Funded Research and Development Centers (FFRDCs) and Government Entities

FFRDCs

FFRDCs are subject to applicable direct competition limitations and cannot propose to this BAA in any capacity unless they meet the following conditions. (1) FFRDCs must clearly demonstrate that the proposed work is not otherwise available from the private sector. (2) FFRDCs must provide a letter, on official letterhead from their sponsoring organization, that (a) cites the specific authority establishing their eligibility to propose to Government BAAs and compete with industry, and (b) certifies the FFRDC's compliance with the associated FFRDC sponsor agreement's terms and conditions. These conditions are a requirement for FFRDCs proposing to be awardees or subawardees.

Government Entities

Government Entities (e.g., Government/National laboratories, military educational institutions, etc.) are subject to applicable direct competition limitations. Government Entities must clearly demonstrate that the work is not otherwise available from the private sector and provide written documentation citing the specific statutory authority and contractual authority, if relevant, establishing their ability to propose to Government BAAs and compete with industry. This information is required for Government Entities proposing to be awardees or subawardees.

Authority and Eligibility

At the present time, ARPA-H does not consider 15 United States Code (U.S.C.) § 3710a Cooperative Research and Development Agreements to be sufficient legal authority to show specific authority establishing an entity's eligibility to propose to Government BAAs and compete with industry. Additional specific authority must be cited to establish eligibility. ARPA-H will consider FFRDC and Government Entity eligibility submissions on a case-by-case basis; however, the burden to prove eligibility for all team members rests solely with the proposer.

3.1.2. Other Applicants

ARPA-H will prioritize awards in accordance with Public Law No. 117-328 (Section 499A(n) of the PHSA). Without limiting the foregoing ARPA-H will prioritize awards to domestic entities (organization and/or individuals) that will conduct funded work in the US. However, non-US entities may participate to the extent such participants comply with nondisclosure agreements, security regulations, export control laws, and other governing statutes applicable under the circumstances. Non-US entities are encouraged to collaborate with domestic US entities. In no case will awards be made to entities organized under the laws of a covered foreign country (as defined in section 119C of the National Security Act of 1947 (50 U.S.C. § 3059)) or entities suspended or debarred from business with the Government.

3.2. ORGANIZATIONAL CONFLICTS OF INTEREST (OCI)

Proposers are required to identify and disclose all facts relevant to potential OCIs involving the proposer's organization and any proposed team member (proposed subawardee). Although the FAR does not apply to OTAs, cooperative agreements, ARPA-H requires OCIs be addressed in the same manner prescribed in FAR subpart 9.5. Regardless of whether the proposer has identified potential OCIs under this section, the proposer is responsible for providing a disclosure with its proposal. The disclosure must include the proposer's, and as applicable, proposed team members' OCI mitigation plans. The OCI mitigation plan(s) must include a description of the actions the proposer has taken, or intends to take, to prevent the existence of conflicting roles that might bias the proposer's judgment and to prevent the proposer from having unfair competitive advantage. The OCI mitigation plan will specifically discuss the disclosed OCI in the context of each of the OCI limitations outlined in FAR 9.505-1 through FAR 9.505-4. The disclosure and mitigation plan(s) do not count toward the page limit.

Agency Supplemental OCI Policy

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

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

- The name of the ARPA-H office receiving the support;
- The prime contract number;
- Identification of proposed team member (proposed subawardee) providing the support; and
- An OCI mitigation plan in accordance with FAR 9.5.

Government Procedures

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

4. Application and Submission Information

4.1. ADDRESS TO REQUEST APPLICATION PACKAGE

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

4.2. CONTENT AND FORM OF APPLICATION SUBMISSION

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

All submissions must be written in English with type not smaller than 12-point font. Smaller font may be used for figures, tables, and charts. Documents submitted must be clearly labeled with the ARPA-H BAA number, proposer organization, and proposal title/proposal short title.

4.2.1. Abstract Format

Proposers to the BAA must submit an abstract. Based on evaluation of the abstract, ARPA-H may request a full proposal from BAA respondents. The cover sheet should be clearly marked "ABSTRACT," and the total length should not exceed six (6) pages in length. The maximum page count excludes the cover page and the Rough Order of Magnitude. The Government will not review pages beyond 6; and any abstract submitted that exceeds six (6) pages will only be reviewed at ARPA-H's discretion. Official transmittal letter is not required.

A. Cover Page

The cover page should follow the same format as the full proposal described in Section 4.2.2.A. The cover page does not count towards the page limit.

B. Concept Summary

Describe the proposed concept with minimal jargon and explain how it addresses the topic area(s) of the BAA.

C. Innovation and Impact

Clearly identify the health outcome(s) sought and/or the problem(s) to be solved with the proposed technology concept. Describe how the proposed effort represents an innovative and potentially revolutionary solution to the technical challenges posed by the BAA. Explain the concept's potential to be disruptive compared to existing or emerging technologies. Describe how the concept will have a positive impact on at least one of ARPA-H's mission areas.

To the extent possible, provide quantitative metrics in a table that compares the proposed technology concept to current and emerging technologies and includes:

- State of the art / emerging technology "baseline"
- Target for proposed technology in its final, commercializable form
- Target for proposed technology at the end of the proposed ARPA-H project

D. Proposed Work

Describe the final deliverable(s) for the project, one or two key interim milestones, and the overall technical approach used to achieve project objectives. Discuss alternative approaches considered, if any, and why the proposed approach is most appropriate for the project objectives. Describe the background, theory, simulation, modeling, experimental data, or other sound engineering and scientific practices or principles that support the proposed approach. Provide specific examples of supporting data and/or appropriate citations to the scientific and technical literature. Identify commercialization challenges to be overcome for the proposed technology to be successful in the health market.

Describe why the proposed effort is a significant technical challenge and the key technical risks to the project. At a minimum, the abstract should address:

- Does the approach require one or more entirely new technical developments to succeed?
- How will technical risk be mitigated?

E. Team Organization and Capabilities

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

F. Rough Order of Magnitude (ROM)

Please include a ROM estimate of timeline and federal funds requested, as well as the total project cost including cost sharing, if applicable. The ROM should also include a breakdown of the work by direct labor, labor rates, subcontracts, materials, equipment, other direct costs (e.g., travel), indirect costs, profit, cost sharing, and any other relevant costs. The below table may be used for this breakdown:

Cost Category	**Amount**
Direct Labor	
Indirect Costs	
Subawardees	
Materials	
Equipment	
Travel	
Other Direct Costs	
Indirect Costs	

Profit	
Total	
Cost Sharing *(if applicable)*	

However, proposers should 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.

4.2.2. Full Proposal Format

Proposals must be in the format given below. The typical proposal should express a consolidated effort in support of one or more related technical concepts or ideas. Disjointed or unrelated efforts should not be included in a single proposal. Proposals shall consist of two volumes: 1) **Volume I, Technical and Management Proposal (composed of 3 parts),** and 2) **Volume II, Cost Proposal**. The Cover Page shall be no more than one (1) page in length. 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. Copies of all documents submitted must be clearly labeled with the ARPA-H BAA number, proposer organization, and proposal title/proposal short title. Volume I, Technical and Management Proposal, may include an attached bibliography of relevant technical papers or research notes (published and unpublished) which document the technical ideas and approach upon which the proposal is based. Copies of not more than three (3) relevant papers may be included with the submission. The bibliography and attached papers are not included in the page counts given below. The submission of other supporting materials along with the proposals is strongly discouraged and will not be considered for review. The maximum page count for Volume 1 is forty (40) pages; excluding the Statement of Work (SOW). However, for all sections, ARPA-H encourages conciseness to the maximum extent practicable. Volume I should include the following components:

A. Volume I, Technical and Management Proposal

Section I: Administrative

Cover Page

1. BAA number (75N99223R0003);
2. Technical area;
3. Proposal title;
4. Prime Awardee/entity submitting proposal;
5. Type of organization, selected among the following categories: LARGE BUSINESS, SMALL DISADVANTAGED BUSINESS, OTHER SMALL BUSINESS", Historically Black Colleges and Universities (HBCUs), Minority Institution (MI), 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

6. Date of submission;
7. Other team members (if applicable) and type of organization for each;
8. Proposal title;
9. Technical point of contact (POC) to include: salutation, last name, first name, street address, city, state, zip code, telephone, email;
10. Administrative POC to include: salutation, last name, first name, street address, city, state, zip code, telephone, email; and
11. Total funds requested from ARPA-H, and the amount of cost share (if any).

Section II: Summary of Proposal

Proposal Content

A. Technical rationale, technical approach, and constructive plan for accomplishment of technical goals in support of innovative claims and deliverable creation. (In the full proposal, this section should be supplemented by a more detailed plan in Section III of the Technical and Management Proposal.)

B. Innovative claims for the proposed research. This section is the centerpiece of the proposal and should succinctly describe the uniqueness and benefits of the proposed approach relative to the current state-of-art alternate approaches.

C. Deliverables associated with the proposed research and the plans and capability to accomplish technology transition and commercialization. Include in this section all proprietary claims to the results, prototypes, intellectual property, or systems supporting and/or necessary for the use of the research, results, and/or prototype. If there are no proprietary claims, this should be stated. For information to be provided regarding intellectual property, see Section 4.2.3 of this BAA.

D. General discussion of other research in this area. Proposers must disclose 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 in the course of such efforts or challenges in securing sources of funding, as applicable.

E. A clearly defined organization chart for the program team. Please also include information describing (1) the programmatic relationship of team member; (2) the unique capabilities of team members; (3) the task of responsibilities of team members; (4) the teaming strategy among the team members; and (5) the key personnel along with the amount of effort to be expended by each person during each year.

Section III: Detailed Proposal Information

A. Executive Summary:

Provide a synopsis of the proposed project, including answers to the following questions:

- What is the proposed work attempting to accomplish or do?
- How is it done today, and what are the limitations?
- What is innovative in your approach?
- What are the key technical challenges in your approach, and how do you plan to overcome these?
- Who or what will be affected, and what will be the impact if the work is successful?
- How much will it cost, and how long will it take?

B. Goals and Impact:

Clearly describe what the team is trying to achieve and the difference it will make (qualitatively and quantitatively) if successful. 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 and any plans to commercialize the technology, transition it to a customer, or further the work.

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 expertise of the team, including any subawardees, 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 strongly encouraged to identify a Project Manager/Integrator to serve as the primary POC to communicate with the ARPA-H PM, IV&V team, and OTA/Grant Officer's Representative equivalent for each award instrument (e.g., Grants Management Specialist), coordinate the effort across co-performer, vendor, and subwardee teams, 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, 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/subawardees of the proposed effort. Include risk management approaches. Describe any formal teaming agreements required to execute this program.

E. Metrics:

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. Statement of Work (SOW) NOT INCLUDED IN PAGE COUNT:

The SOW 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 SOW must not include proprietary information.

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, subawardee(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 SOW be developed so that each TA and Phase of the program is separately defined.

G. Schedule and Milestones:

Provide a detailed schedule showing tasks (task name, duration, work breakdown structure element as applicable, performing organization), milestones, and the interrelationships among tasks. The task structure must be consistent with that in the SOW. Measurable milestones should be clearly articulated and defined in time relative to the start of the project.

H. Technology Transfer Plan:

Provide information regarding the types of partners (e.g., government, private industry) that will be pursued and submit a timeline with incremental milestones toward successful engagement. The plan should include a description of how ARPA-H will be included in

the development of potential technology transfer relationships. If the Technology Transfer Plan includes the formation of a start-up company, a business development strategy must also be provided.

B. Volume II, Cost Proposal

(1) All proposers, including FFRDCs, must submit the following:

Cover Page

1. BAA number (75N99223R0003);
2. Technical area;
3. Prime Awardee/entity submitting proposal;
4. Type of organization, selected among the following categories: LARGE BUSINESS, SMALL DISADVANTAGED BUSINESS, OTHER SMALL BUSINESS", Historically Black Colleges and Universities (HBCUs), Minority Institution (MI), OTHER EDUCATIONAL, OR OTHER NONPROFIT (including non-educational government entities)
5. Proposer's reference number (if any);
6. Other team members (if applicable) and type of organization for each;
7. Proposal title;
8. Technical POC to include: salutation, last name, first name, street address, city, state, zip code, telephone, email;
9. Administrative POC to include: salutation, last name, first name, street address, city, state, zip code, telephone, and email;
10. Award instrument requested: Cooperative Agreement or OTA;
11. Place(s) and period(s) of performance;
12. Total proposed cost separated by base and option(s) (if any);
13. Name, address, and telephone number of the proposer's cognizant auditor (as applicable);
14. Date proposal was prepared;
15. Unique Entity Identification (UEI) number;
16. Commercial and Government Entity (CAGE) Code;
18. Proposal validity period (Minimum of 120 days).

Cost Proposal Information

The Government requires proposers use the MS Excel ARPA-H Standard Cost Proposal Spreadsheet in the development of cost proposals[4]. This spreadsheet will be provided to proposers if the Government recommends they submit a full proposal. 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. This cost proposal spreadsheet should be used by the prime organization and all subawardees. In addition to using the cost proposal spreadsheet,

[4] University proposers requesting a cooperative agreement do not need to use the Standard Cost Proposal Spreadsheet. Instead, a proposed budget and justification may be provided solely using the SF-424 Research & Related Budget forms provided via https://www.grants.gov.

the cost proposal still must include all other items required in this announcement that are not covered by the editable spreadsheet. Subawardee cost proposal spreadsheets may be submitted directly to the Government by the proposed subawardee via email to the address in the Part I *Overview Information*.

NOTE: Non-conforming submissions that do not address the TAs as outlined under Section 1.2.1 and/or do not follow instructions herein may be rejected without further review.

a) Cost Breakdown Information and Format

Detailed cost breakdown to include[5]:

1. **Total Program Costs**
    a. Broken down by major cost items (e.g., direct labor, including labor categories; subagreements, materials; other direct costs; overhead charges, etc.)
    b. Further broken down by task and phase
2. **Major Program Tasks by Fiscal Year**
3. **An Itemization of Major Subagreements**
    a. In the same detail as the total program cost breakdown, and equipment purchases.
4. **Equipment**
    a. Documentation supporting the reasonableness of the proposed equipment costs (e.g., vendor quotes, past purchase orders/purchase history, detailed estimates from technical personnel, etc.) shall be provided.
5. **Itemization of Any Information Technology (IT) Purchases** (as defined by FAR 2.101)
    a. Documentation supporting the reasonableness of the proposed equipment costs (e.g., vendor quotes, past purchase orders/purchase history, detailed estimates from technical personnel, etc.) shall be provided.
6. **Summary of Projected Funding Requirements**
    a. By month
7. **Any Industry Cost-Sharing (if applicable)**
    a. Include the source, nature, and amount
8. **Identification of Pricing Assumptions** (which may require incorporation into the resulting award instrument)
    a. Use of Government Furnished Property/Facilities/Information, access to Government Subject Matter experts, etc.

Tables included in the cost proposal must be in editable (e.g., MS Excel) format with calculation formulas intact.

[5] While cost and pricing data is required, certified cost and pricing data is not required for any award instruments resulting from this BAA.

NOTE: If PDF submissions differ from the Excel submission, the PDF will take precedence.

C. Supporting Cost and Pricing Data

Respondents to the BAA should include supporting cost and pricing information in sufficient detail to substantiate the summary cost estimates and should include a description of the method used to estimate costs and supporting documentation. For other direct costs (ODCs) (e.g., equipment, IT) greater than $5,000 provide screenshots/quotes.

Subawardee Proposals

The awardee is responsible for compiling and providing all subawardee proposals for the Grants or OTA Officer as applicable. Subawardee proposals should include Interdivisional Work Transfer Agreements or similar arrangements between the awardee and divisions within the same organization as the awardee. Where the effort consists of multiple portions which could reasonably be partitioned for purposes of funding, these should be identified as option periods with separate cost estimates for each.

All proprietary subawardee proposal documentation, prepared at the same level of detail as that required of the respondent's proposal and which cannot be uploaded with the proposed awardee's proposal, shall be provided to the Government either by the proposer or by the subawardee when the proposal is submitted. Subawardee proprietary proposals may be submitted directly to the Government. See Section 4.2.4. of this BAA for Proposal Submission information.

D. Other Documents

Proposers should include any other required documents, as applicable, in the cost proposal. This may include OCI disclosures, OCI mitigation plans, Human Subjects and Animal Subjects Research documentation, intellectual property representations and assertions, etc.

4.2.3. Additional Proposal Information

Proprietary Markings

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.

Human Subjects Research (HSR)

All entities applying for funding that involves 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 (https://www.hhs.gov/ohrp/index.html). All human subjects research must be reviewed and approved by an Institutional Review Board (IRB), as applicable under 45 CFR § 46. The 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 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 personnel directly involved with human subjects research. Funding cannot be used toward human subjects research until ALL approvals are granted.

Animal Subjects Research

Award recipients performing research, experimentation, or testing involving the use of animals shall comply with the laws, regulations, and policies on animal acquisition, transport, care, handling, and use as outlined in: (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[6] , which incorporates the "U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training,"[7] and "Guide for the Care and Use of Laboratory Animals" (8th Edition).[8] "

For all proposed research anticipating animal use, proposals should briefly describe plans for Institutional Animal Care and Use Committee (IACUC) review and approval.

Section 508 of the Rehabilitation Act (29 U.S.C. § 749d)/FAR 39.2

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

Cooperative Agreement Summary

Proposers requesting cooperative agreements awards must submit a Project Abstract Summary (use current version in Grants.gov). The one (1) page summary may be publicly posted and

[6] olaw.nih.gov/sites/default/files/PHSPolicyLabAnimals.pdf
[7] olaw.nih.gov/policies-laws/gov-principles.htm
[8] olaw.nih.gov/sites/default/files/Guide-for-the-Care-and-Use-of-Laboratory-Animals.pdf

explains the program or project to the public. The proposer should sign the bottom of the summary confirming the information in the abstract is approved for public release. Proposers are advised to provide both a signed PDF copy, as well as an editable (e.g., Microsoft word) copy. Summaries contained in cooperative agreements proposals that are not selected for award will not be publicly posted. The document will only be requested if a full proposal is requested.

Note: This does not apply to OTAs.

Intellectual Property

All proposers must provide a good faith representation that the proposer either owns or possesses the appropriate licensing rights to all intellectual property that will be utilized under the proposed effort. The information will be requested as part of a full proposal request.

Proposers responding to this BAA requesting a cooperative agreement or OTA shall follow the applicable laws, rules, and regulations governing these various award instruments, but, in all cases, should appropriately identify any desired restrictions on the Government's use of any Intellectual Property contemplated under the award instrument in question. This includes both noncommercial items and commercial items. Respondents are encouraged to use a format similar to that shown in the table below. If no restrictions are intended, then the proposal should state "NONE."

Technical Data Computer Software To be Furnished With Restrictions	Summary of Intended Use in the Conduct of the Research	Basis for Assertion	Asserted Rights Category (e.g., Unlimited, Limited, Restricted, or negotiated, as defined in FAR 27.401)	Name of Person Asserting Restrictions
(LIST)	(NARRATIVE)	(LIST)	(LIST)	(LIST)

System for Award Management (SAM) and Unique Identifier Requirements

Regardless of award type, all proposers must be registered in SAM before submitting an abstract International entities can register in SAM by following the instructions in this link: https://www.fsd.gov/sys_attachment.do?sys_id=c08b64ab1b4434109ac5ddb6bc4bcbb8.

4.2.4. Submission Information

Proposers are responsible for submitting abstracts and proposals to the electronic Contract Proposal Submission (eCPS) website at https://ecps.nih.gov/ and ensuring receipt by the date and time specified. Proposers must use this electronic transmission method. No other method of abstract and proposal submission is permitted. (b) Instructions on how to submit a proposal into eCPS are available at https://ecps.nih.gov/howtosubmit. Proposers may also reference Frequently Asked Questions regarding online submissions at https://ecps.nih.gov/faq. Be advised that registration is required to submit an abstract into eCPS and registration may take several business

days to process. It is highly recommended offerors plan to register through eCPS well in advance of the abstract submission deadline, late abstract submissions resulting from delays with eCPS registration will not be accepted or considered.

All abstracts and full proposals requesting OTAs must be received electronically to eCPS (https://ecps.nih.gov) by the due dates outlined in Part I., *Overview Information* of this BAA. As noted below, full proposals requesting cooperative agreements must be submitted in www.Grants.gov.

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

A. Abstract Submission

Refer to Section 6.1.1. for how ARPA-H will notify proposers as to whether it recommends or discourages submission of a full proposal.

B. Proposal Submission

Refer to Section 6.1.2 for how ARPA-H will notify proposers as to whether their proposal has been selected for potential award.

(1) Solely For Proposers Requesting Cooperative Agreements

Full proposal applications must be submitted in https://www.grants.gov/. In addition to the volumes requested elsewhere in this BAA, proposers submitting a requested full proposal must also submit the three forms listed below. The forms do not count toward the page limitations.

Form 1: SF 424 *Research and Related (R&R) Application for Federal Assistance*, available on the Grants.gov website at https://www.grants.gov/web/grants/forms/r-r-family.html. This form must be completed and submitted.

To evaluate compliance with Title IX of the Education Amendments of 1972 (20 U.S.C. § 1681 et seq.), HHS is collecting certain demographic and career information to be able to assess the success rates of women who are proposed for key roles in applications in science, technology, engineering, or mathematics disciplines. HHS is using the forms below to collect the necessary information to satisfy these requirements. Detailed instructions for each form are available on Grants.gov.

Form 2: The Research and Related Senior/Key Person Profile (Expanded) form, available on the Grants.gov website at https://www.grants.gov/web/grants/forms/r-r-family.html, will be used to collect the following information for all senior/key personnel, including Project Director (PD)/PI and Co-Project Director/Co-PI, whether or not the individuals' efforts under the project are funded by HHS. The form includes 3 parts: the main form administrative information, including the Project Role, Degree Type and Degree Year; the biographical sketch; and the current and pending support. The biographical sketch and current and pending support are to be provided as attachments:

- Biographical Sketch: Mandatory for PDs and PIs, optional, but desired, for all other Senior/Key Personnel. The biographical sketch should include information pertaining to the researchers:
    - Education and Training.
    - Research and Professional Experience.
    - Collaborations and Affiliations (for conflicts of interest).
    - Publications and Synergistic Activities.

- Current and Pending Support: Mandatory for all Senior/Key Personnel including the PD/PI. This attachment should include the following information:
    - A list of all current projects the individual is working on, in addition to any future support the individual has applied to receive, regardless of the source.
    - Title and objectives of the other research projects.
    - The percentage per year to be devoted to the other projects.
    - The total amount of support the individual is receiving in connection to each of the other research projects or will receive if other proposals are awarded.
    - Name and address of the agencies and/or other parties supporting the other research projects
    - Period of performance for the other research projects.

Additional senior/key persons can be added by selecting the "Next Person" button at the bottom of the form. If ARPA-H receives an application without the required information, ARPA-H may determine that the application is incomplete and may cause your submission to be rejected and eliminated from further review and consideration under this BAA. ARPA-H reserves the right to request further details from the applicant before making a final determination on funding the effort.

Form 3: Research and Related Personal Data, available on the Grants.gov website at https://www.grants.gov/web/grants/forms/r-r-family.html. Each applicant must complete the name field of this form, however, provision of the demographic information is voluntary. Regardless of whether the demographic fields are completed or not, this form must be submitted with at least the applicant's name completed.

4.3. Funding Restrictions

Preaward costs will not be reimbursed unless a preaward cost agreement is negotiated prior to award.

4.4. Questions

Interested entities may submit questions to the BAA Coordinator. Answers to questions received will be posted to www.SAM.gov. ARPA-H will likely post answers to all relevant non-duplicative questions at intervals.

5. Application Review Information

5.1. EVALUATION CRITERIA

Abstracts will be evaluated based only on evaluation criteria #1, #2, and #4, in descending order of importance; however, the ROM will only be reviewed for reasonableness. A realism analysis may also be performed at the Government's discretion. Abstracts will undergo an initial review for responsiveness.

Abstracts that are outside the scope of the BAA will not be evaluated further. In addition, Abstracts that do not meet the submission requirements or do not contain one or more of the required items listed above may be deemed nonresponsive and will not be evaluated further.

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

5.1.1. Evaluation Criteria #1: Overall Scientific and Technical Merit

The proposed technical approach is innovative, feasible, achievable, and complete. Task descriptions and associated technical elements provided are complete and in a logical sequence with all proposed deliverables clearly defined such that a final outcome that achieves the goal can be expected as a result of award. The proposal identifies major technical risks and planned mitigation efforts are clearly defined and feasible.

5.1.2. Evaluation Criteria #2: Proposer's Capabilities and/or Related Experience

The proposed technical team has the expertise and experience to accomplish the proposed tasks. The proposer's prior experience in similar efforts clearly demonstrates an ability to deliver products that meet the proposed technical performance within the proposed budget and schedule. The proposed team has the expertise to manage the cost and schedule. Similar efforts completed/ongoing by the proposer in this area are fully described including identification of other Government entities.

5.1.3. Evaluation Criteria #3: Potential Contribution and Relevance to the ARPA-H Mission

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 currently unmet need within biomedicine and improve health outcomes. Degree to which the proposed project has the potential to transform biomedicine. Potential for the project to take an interdisciplinary approach.

5.1.4. Evaluation Criteria #4: Reasonableness/Realism/Funding Availability/Affordability

Price analysis will be performed on each abstract / proposal to ensure the reasonableness of the overall price. In addition, cost realism analysis may be performed to ensure proposed costs are realistic for the technical and management approach, accurately reflect the technical goals and

objectives of this BAA, the proposed costs are consistent with the proposer's SOW and reflect a sufficient understanding of the costs and level of effort needed to successfully accomplish the proposed technical approach. The costs for the prime proposer and proposed subawardees will 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 and the basis for the estimates). In addition, the evaluation will take into consideration the extent to which the proposed intellectual property (IP) rights structure will potentially impact the Government's ability to transition the technology.

It is expected that the effort will leverage all available relevant prior research to obtain the maximum benefit from the available funding. For efforts with a likelihood of commercial application, appropriate direct cost sharing may be a positive factor in the evaluation for an OTA. 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 be in a more competitive posture. ARPA-H discourages such cost strategies.

5.2. REVIEW OF ABSTRACTS AND FULL PROPOSALS

5.2.1. Review Process

It is ARPA-H policy to ensure impartial, equitable, comprehensive abstract/proposal evaluations based on the evaluation criteria listed in Section 5.1. and to select the source(s) whose proposed solution meets the Government's technical, policy, and programmatic goals.

ARPA-H will conduct a scientific/technical review of each conforming abstract/proposal. Conforming abstracts/proposals comply with all requirements detailed in this BAA; abstracts/proposals that fail to do so may be deemed non-conforming and may be removed from consideration. Abstracts/proposals will not be evaluated against each other since they are not submitted in accordance with a common work statement. ARPA-H's intent is to review abstracts/proposals as soon as possible after they arrive; however, abstracts/proposals reviews may be delayed (e.g., conducted periodically for administrative reasons). ARPA-H reserves the full period of this BAA plus 45 days for review of proposals.

Award(s) will be made to proposers whose abstracts/proposals are determined to be the most advantageous to the Government, consistent with instructions and evaluation criteria specified in the BAA, and availability of funding.

5.2.2. Handling of Source Selection Information

ARPA-H policy is to treat all submissions as source selection information (see FAR 2.101 and 3.104), and to disclose their contents only for the purpose of evaluation. Restrictive notices notwithstanding, during the evaluation process, submissions may be handled by support contractors for administrative purposes and/or to assist with technical evaluation. All ARPA-H support contractors performing this role are expressly prohibited from performing ARPA-H sponsored technical research and are bound by appropriate nondisclosure agreements. Subject to the restrictions set forth in FAR 37.203(d), input on technical aspects of the abstracts/proposals

may be solicited by ARPA-H from non-Government consultants/experts who are strictly bound by the appropriate non-disclosure requirements.

Information may also be provided to Courts and the U.S. Government Accountability Office, to the extent that the information is necessary for compliance with federal law or a court order.

5.2.3. Federal Awardee Performance and Integrity Information (FAPIIS)

Per 41 U.S.C. § 2313, as implemented by FAR 9.103 and 2 CFR § 200.205, prior to making an award above the simplified acquisition threshold, ARPA-H is required to review and consider any information available through the designated integrity and performance system (currently FAPIIS). Entities can comment on any information about themselves entered in the database, and ARPA-H will consider any comments, along with other information in FAPIIS or other systems, prior to making an award.

6. Award Administration Information

6.1. SELECTION NOTICES AND NOTIFICATIONS

6.1.1. Abstracts

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

1. ARPA-H does not recommend the proposer moves forward with a full proposal;
2. ARPA-H requests that the proposer submit a full proposal;
3. ARPA-H will not recommend a full proposal at this time but will place the abstract in the "basket" for potential future consideration; or
4. ARPA-H will contact the proposer for explanation on any unclear elements in the submitted abstract in order to determine whether the abstract will be selected or not.

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

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

6.1.2. Full Proposals

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

1. ARPA-H has not selected the proposal; or
2. ARPA-H has selected the proposal for funding pending award negotiations, in whole or in part. Official notifications will be sent via email to the Technical POC and/or Administrative POC identified on the proposal coversheet.

6.2. ADMINISTRATIVE AND POLICY REQUIREMENTS

6.2.1. Meeting and Travel Requirements

There will be a program kickoff meeting and all key participants are required to attend. Performers should also anticipate regular program-wide PI Meetings and/or periodic site visits at the PM's discretion.

6.2.2. Award Clauses, Terms and Conditions

Specific terms and conditions will be negotiated for each award instrument.

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 to include monthly financial status reports, monthly technical status reports, quarterly 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. If applicable based on funding amount, reporting requirements specified in 45 CFR Part 75 Appendix XII will be incorporated into the Cooperative Agreement.

6.4. ELECTRONIC SYSTEMS

6.4.1. Payment/Funding Receipt

For OTAs, performers will be required register in and to submit invoices for payment directly to the Invoicing Processing Platform (IPP) at https://www.ipp.gov, unless an exception applies.

For cooperative agreements, the Government anticipates performers will be required to register in the Payment Management Services system at https://pms.psc.gov.

6.4.2. i-Edison

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

7. Agency Contacts

The BAA Coordinator for this effort may be reached at NITRO@ARPA-H.gov.

8. Other Information

ARPA-H will host a Proposers' Day in support of the NITRO Program on the date listed in Part I., *Overview Information* of this BAA. Interested proposers are not required to attend, and materials formally presented at Proposers' Day will be posted to www.SAM.gov.

ARPA-H will not reimburse potential proposers for participation at the Proposers' Day or time and effort related to submitting abstracts/full proposals.