

Broad Agency Announcement (BAA)
Precision Surgical Interventions (PSI)
Health Science Futures (HSF) Office
75N99223R0004
21 August 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 – Precision Surgical Interventions (PSI)**
- **Announcement Type –** Initial Announcement
- **Funding Opportunity Number –** 75N99223R0004
- **Assistance Listing Number –** 93.384
- **NAICS: 541714 -** Research and Development in Biotechnology (except Nanobiotechnology)

- **Dates**
  - Posting Date: **August 21, 2023**
  - Proposers' Day: **September 07, 2023**
    - Proposers' Day Registration Deadline: **August 28th, 2023, 12:00 PM EDT**
  - Abstract Due Date and time: **September 21st, 2023, 12:00 PM EDT**
  - Proposal Due Date and time: **November 20th, 2023, 5:00 PM EST**
- **Concise description of the funding opportunity –** Despite recent technological advances, there are no practical solutions for some longstanding challenges faced by surgeons in the operating room. Cancer is oftentimes indistinguishable from normal tissue, and occasionally gets left behind, requiring reoperations. Critical anatomical structures such as nerves, blood vessels, lymph nodes or lymph ducts also look like surrounding tissue, and can be accidentally injured during surgeries, leading to long-term patient morbidity. The Precision Surgical Interventions (PSI) program aims to develop technologies to aid surgeons to complete procedures with high accuracy, dramatically reducing inadvertent errors and reoperation rates. More specifically, PSI seeks to develop intraoperative end-to-end solutions for enhanced visualization of cancerous tissues. These solutions, available at the bedside (imaging the resected specimens), or in vivo (imaging the resection cavity), will allow physicians to visualize with microscopic precision where cancer ends, enabling them to accurately complete all oncological surgeries and reduce reoperations. Secondly, PSI proposes to develop intraoperative systems that enable surgeons to better visualize critical structures in real time. Nerves, blood vessels or other anatomical structures that are not easily visible (e.g., parathyroid glands, urethra, lymph node ducts) will be preserved, thus sparing patients from long-term consequences.
- **Anticipated individual awards –** Multiple awards are anticipated.
- **Potential award instruments –** Cooperative Agreements or Other Transactions (OT)
- **Agency Contact –** All inquiries shall be sent to PSI@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 Title 2 of the Code of Federal Regulations (CFR) § 200.203 and is in accordance with section 499A of the Public Health Service Act. Advanced Research Projects Agency for Health (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 strategies that address current surgical challenges and will improve patient outcomes.

Specifically excluded are: 1) proposals that represent an evolutionary or incremental advance in the state of the art 2) partial or incomplete solutions (e.g., contrast agents that label one single type of cancer, microscopic images that are not automatically analyzed and classified, thus requiring a pathologist on staff; imaging and classification approaches that take more than 15 minutes to deliver results) 3) performers unable to address the objectives of the program, 4) 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

In modern surgical practice, it is still extremely challenging to distinguish cancer and critical anatomical structures (such as nerves, blood vessels, etc.) from normal surrounding tissue. This inherent lack of contrast results in high reoperation rates and accidental injuries, which can plague patients for years and cost the American healthcare system more than $1 billion per year.

Roughly two million Americans are newly diagnosed with cancer every year. For many, tumor resection is the first-line treatment, and should result in negative (“clean”) margins, i.e., no cancer is left behind. Currently, the gold standard for tumor margin evaluation is a pathological examination of the resected specimen by a board-certified pathologist, usually days after the initial surgery. If the margins are positive, patients generally undergo reoperation. The estimated costs for reoperations due to positive margins after breast cancer surgeries alone are >$500 million/year. Reoperation is unfortunately not always possible, and patients are offered adjuvant treatment instead (such as chemotherapy or radiation therapy). Survival rates, however, decrease significantly with positive margins; for example, the 5-year survival rate for prostate cancer patients decreases from 71% with negative margins to 42% with positive margins.

The inability to visualize critical anatomical structures also has dramatic consequences for patients undergoing surgery. Unintentional damage or removal of critical structures can cause serious

complications both during and after the procedure. Damaged nerves lead to surgically induced neuropathic pain, which occurs in roughly 10 – 50% of patients, with 2 – 10% experiencing severe pain; nicked blood vessels result in bleeding that extends procedures and hospital stays and can threaten the patient's life; urethra damage can lead to urinary incontinence; parathyroid gland removal can cause hypocalcemia; damage to lymph ducts can cause lymphedema. While some damage to critical structures is both inevitable and planned, many injuries are inadvertent and can be avoided if the surgeon could properly visualize these structures.

The aim of the Precision Surgical Interventions (PSI) program is to catalyze advancements in the surgical field, with the final goals of providing the surgeon with revolutionary tissue visualization and classification tools, thus increasing surgical precision, decreasing reoperations, and improving patient care. PSI seeks to develop technologies that improve surgical outcomes through two technical areas. Technical Area 1 (TA1) aims to develop systems that image tumors intraoperatively at microscopic scales. TA1 requires performers to develop an end-to-end pathology system that operates at the bedside (TA1-A) or *in vivo* (TA1-B) and classifies margins as positive or negative within 15 minutes, without a pathologist. Technical Area 2 (TA2) aims to develop devices and software to localize and visualize critical anatomical structures (nerves, blood vessels and organs) in 3D during surgery. TA2 requires performers to develop a real-time, end-to-end system that enables visualization of critical structures buried up to 1 cm deep. In accordance with the equity goals of ARPA-H, PSI will require solutions that will be easily accessible to all hospital settings.

1.2 TECHNICAL APPROACH AND STRUCTURE

1.2.1. Technical Areas (TAs)

The PSI program will develop novel intraoperative devices and tools to decrease the reoperation rate in oncological surgeries and the rate of accidental damage to critical structures in all surgeries. To accomplish this, the PSI Program is focused on two (2) Technical Areas:

- **Technical Area 1 (TA1): Cancer localization.**
  Two alternative options for this technical area exist, as described below. Proposers must select one (1) single option.
  - **TA1-A (In vitro pathology):** Development of end-to-end solutions, including devices and software, for intraoperative **microscopic** imaging of a resected specimen and automated image classification. Use of existing staining agents, or development and optimization of new staining agents, that can be *used once the specimen is removed from the body*, are also allowed under this aim.
  - **TA1-B (In vivo pathology):** Development of end-to-end solutions, including devices and software, for intraoperative **microscopic** imaging of the resection cavity and automated image classification. Use of existing, Food and Drug Administration (FDA)-approved contrast agents, as well as development and optimization of new contrast agents, capable of labeling the cancer cells or the cells in the tumor microenvironment (*in vivo*) are also allowed under this aim.
- **Technical Area 2 (TA2): Healthy structure localization**. Development of devices and software capable of sensing structures of interest at their depth, integrated with surgical

tools and/or surgical workflow. Use of existing, FDA-approved contrast agents, as well as development and optimization of new contrast agents capable of labeling the structures of interest *in vivo*, are also allowed under this aim.

Proposal details: Performers will have the option of submitting proposals that address TA1-A or TA1-B or TA2. If two equally rated proposals address TA1-A and TA1-B, respectively, the one addressing TA1-B will be given preference. A group (e.g., a contrast agent or digital pathology developer) may participate in two proposals but cannot be the *prime (contact)* proposer on both. Proposals may only address TA1-A, TA1-B, or TA2, with the single exception of a combined response to TA1-B and TA2, in which a significant component of the technical solution (e.g., microscopy method or contrast agent) addresses both Technical Areas.

Proposals that only provide parts of the solutions above (i.e., just an agent, or just a device, or just a classification algorithm), and not an end-to-end solution, will be deemed non-conforming and rejected without further review.

TA1: Cancer localization

Surgical resection is oftentimes the first line of treatment after cancer diagnosis. Even with thorough preoperative imaging and surgical planning, it is difficult to achieve complete tumor resection, leaving no cancer cells behind, as cancerous tissue cannot be easily distinguished from normal tissue. The surgeon removes a volume of tissue believed to encompass the entire tumor, closes the patient, then sends the resected tissue for pathological examination. Formalin-Fixed Paraffin-Embedded (FFPE) ~4 mm thick slices are obtained from the surgical sample; the surface of these slices is examined under a microscope by a pathologist days later. It is not uncommon for tumor cells to be found at the edge of the surgical specimen, indicating that the tumor was not entirely resected. The patient then usually undergoes a second surgery to remove additional tissue, increasing anxiety, morbidity, and healthcare costs. In some cases, such as prostate cancer, reoperation is not the standard of care, as abdomen reorganization after surgery makes it difficult to locate the effective match to the positive margin identified by the pathologist. Systemic adjuvant therapies are offered instead, but the survival of patients with positive margins after cancer surgery is significantly lower than that of patients with negative margins.

A solution to the above problem is the use of intraoperative frozen section examination during surgery. In this approach, a pathologist is on standby during surgeries for which frozen sections are requested. Verbal communication between the surgeon and pathologist is usually needed to identify the potential regions of interest. Surgery is interrupted, and the specimen is sent for pathology examination; at least 20 minutes are needed for inspection of a single slice by the pathologist, assuming a simple case. Longer time is required if multiple slices need to be inspected, or if it is a complicated case. Freezing tissue introduces artifacts, and the results of frozen section analysis do not always coincide with the results of FFPE analysis, which remains the gold standard. Although practices and results vary between hospitals, surgeons and pathologists, certain types of surgeries (e.g., for breast cancer) have generally moved away from frozen section analysis. Frozen sections are also not practical in limited resource settings, where a pathologist may not be on call for the duration of the surgery. Even when frozen sections are used, given that only a few slices are examined, FFPE may still indicate additional positive margins, prompting further reoperations.

The vision of the PSI program is that the developments performed under TA1 will reduce positive margins during oncological surgery to no more than 2%. TA1 will require investigators to provide end-to-end solutions, in which either the surgical specimen or the resection cavity are imaged at microscopic resolution. In addition, once images are acquired, an automated analysis will be made, determining if margins contain cancer cells. If such cells exist, their location needs to be identified, allowing the surgeon to further re-excise tissue (during the same initial surgery) if needed. Two implementations of this technical area are envisioned (TA1-A and TA1-B) as described below. Investigators are expected to select one of the two.

TA1-A: In vitro pathology. Devices and software for intraoperative **microscopic imaging of resected specimens** and automated image classification will be developed. While it is preferred that the end-to-end solution remain label free for cost and ease-of-use reasons, performers may also propose to use or develop agents to stain the specimen *once removed from the body*. Agents may include existing, validated staining agents (such as hematoxylin and eosin), those under different stages of development, or brand-new concepts. If new stains are proposed, it is desired that they be cancer-type agnostic, enabling them to be used across the cancer spectrum, and not for one cancer type alone.

The end-to-end solution for automated in vitro digital pathology must meet the following minimum specifications:

- It must accommodate samples as large as 10 cm x 10 cm x 10 cm (or an equivalent spherical surface)
- Imaging of the entire sample surface is preferred, without sample grossing. If the specimen is grossed, it must provide margin information no sparser than one slice every 4 mm over the volume of the sample (e.g., for a sample of 10 cm on the longest axis, it must be able to image 25 slices). Since margin information alone is needed, readout may be performed only within 1 cm of the edge, should slices be imaged in cross-section.
- The samples must be fresh, not frozen.
- It must complete the evaluation of the entire sample in less than 10 minutes, including imaging and classification time. An additional 5 minutes for sample preparation may be used.
- Imaging resolution must be equal to or better than 0.5 μm. A multiscale approach, in which the majority of the sample is imaged at 1-2 μm, while suspicious regions automatically identified in the lower resolution images are then imaged at 0.5 μm, will also be considered acceptable.
- The solution chosen must be generally applicable. To ensure the broad applicability of the approach while keeping program effort reasonable, demonstration in two cancer types is required. For the first cancer, breast, colorectal, head and neck or ovarian cancers should be selected (with the listing order above defining preference order). Any cancer type can be selected for the second validation case. Proposals should include relevant rationale for the choice of the second cancer.
- If breast cancer is chosen, additional imaging and classification of sentinel lymph node status is encouraged but not required.

- Once images are acquired, classification must be automated (e.g., using a machine learning algorithm). A pathologist must not be required in the operating room.
- If the margins are positive, the classification algorithm needs to provide the surgeon with the location of the positive margin, which must have a clear correspondence to the location where the surgeon needs to re-excise.
- Final sensitivity, demonstrated in surgical specimens from ≥150 human surgeries, for each of the two cancer types selected, should be ≥98% and specificity ≥95%.
- While the primary outcome is resection margin status (2 weeks after primary surgery), secondary outcome measures (listed below) need to be documented.
    - Reoperation rate (Time Frame: 2 months after primary surgery). The decision for a reoperation is determined by the surgeon. Data regarding reoperation and reason for reoperation must be recorded.
    - Operation time (Time Frame: Immediately after primary surgery). Operation time is defined by time from incision to closure, which will be obtained from anesthesia report.
    - Cost effectiveness (Time Frame: 3 months after primary surgery). Data for in-hospital cost including cost for re-excision will be collected. Additional costs due to elongated surgery time and labor costs from the pathology department will also be calculated and included.
    - Resection volume (Time Frame: 3 months after primary surgery). Resected volume is calculated from gross specimen measurements of pathology report (volume = width/2 * height/2 * depth/2). When additional resection is performed, resected volumes are reported separately.
- If the metrics/number of subjects above are not meaningful for a particular case, proposing teams are expected to provide their own metrics and describe the quantitative improvement those metrics represent over the state-of-the-art. Power analysis calculations are needed to support the proposed metrics.
- The ground truth of the pathological read should be set by three pathologists using FFPE.
- Since the imaging/validation process is not expected to interfere with standard of care, it is expected that testing of human samples can be completed under IRB approval by the end of the performance period, and not require FDA approvals.
- 510k/PMA/de novo submission for the device-software combination.

TA1-B: In vivo pathology. Devices and software for intraoperative **microscopic imaging of the resection cavity** and automated image classification will be developed. While it is preferred that the end-to-end solution remain label free for cost and ease-of-use reasons, performers may also propose to use or develop contrast agent to label cancer macroscopically in vivo. Labeling may come in injectable, oral, paint-on or spray-on form. Contrast agents may include existing, FDA-approved agents (such as Indocyanine Green (ICG), Cytalux or Gleolan), contrast agents already under development, or brand-new concepts. If new agents are proposed, it is desired that they be cancer-type agnostic, targeting general cancer hallmarks (e.g., CD24, B7-H3 markers, annexin, fibroblasts or macrophages, etc.), enabling them to be used across the cancer spectrum, and not for one cancer type alone. Combinations of contrast agents targeting multiple cancer hallmarks (but labeled in a way that enables single querying) are encouraged. Specific solutions (e.g., for prostate cancer), although not preferred, will also be considered, provided a thorough explanation is given as to why a more general solution is not appropriate.

The end-to-end solution for automated *in vivo* digital pathology must meet the following minimum specifications:

- While it is desired that the proposed solution image the entire resection cavity at microscopic resolution, it is understood that motion artifacts and the sheer amount of data may make this impractical. Alternatively, rational/deterministic down-selection from the entire field of view (FOV) to a limited number of regions of interest (ROIs) can be performed. The opinion of a surgeon as to which margin may be positive does not count as a deterministic factor, but selective labeling of a given ROI by a targeted contrast agent does. These ROIs, no less than 2 cm x 2 cm each (or an equivalent circular surface), will then be imaged one at a time.
- It must complete the evaluation of each ROI in less than 3 minutes, or of the entire FOV in less than 10 minutes. Imaging time for ROIs smaller than 2 cm x 2 cm will be reduced proportional to the ratio of surface areas.
- A support/fixation solution needs to be included in the design, such that an operator is not required to hold on to the imaging probe during the imaging time.
- Since the imaging device will be present in the surgical field, sterility needs to be addressed, while not significantly increasing costs.
- Imaging resolution must be equal to or better than 0.5 μm.
- If a contrast agent/contrast agent cocktail will be used for macroscopic tissue labeling in vivo, >90% of the relevant cancers need to be labeled. For example, if prostate cancer is the main target of the proposal, the agent/cocktail should label 90% of the prostate cancers. Labeling efficiency for the given agent/cocktail for the second type of cancer studied should be >70%. Alternatively, a different agent/combination may be used for the second cancer type studied, although cross-cancer agents are preferred.
- The solution chosen must be generally applicable. To ensure the broad applicability of the approach while keeping program effort reasonable, demonstration in two cancer types is required. For the first cancer, prostate, breast or ovarian cancers should be selected (with the listing order above defining preference order). Any cancer type can be selected for the second validation case. Proposals should include relevant rationale for the choice of the second cancer.
- If breast cancer is chosen, additional classification of sentinel lymph node status is encouraged but not required.
- If prostate cancer is chosen as the proof-of-concept demonstration, the proposed device needs to be integrated with the surgical robot that has become standard of care for prostate surgeries. Care must be taken such as the proposed solution fits within standard laparoscopic openings.
- Once images are acquired, classification needs to be automated (using, e.g., a machine learning algorithm). A pathologist must not be required in the operating room.
- If margins are positive, the classification algorithm needs to provide the surgeon with the location of the positive margin.
- Final sensitivity should be ≥98% and specificity ≥95%, demonstrated in relevant animal models of the chosen cancer.
- If the metrics/number of subjects above are not meaningful for a particular case, proposing teams are expected to provide their own metrics and describe the quantitative improvement

those metrics represent over the state-of-the-art. Power analysis calculations are needed to support the proposed metrics.
- The ground truth of the pathological read should be set by one pathologist using FFPE.
- Since the validation process could interfere with standard of care, it is expected that human testing cannot be completed under IRB approval alone, requiring FDA approvals.
- If a contrast agent/contrast agent cocktail is used, to ensure broad clinical availability, it will go through the FDA approval process on its own, not tied to the device and software.

To achieve the goals of the program, performers may propose a variety of technical approaches to classify tumor margins in vitro or in vivo. They may include, but are not limited to:
- Contrast agents (optical, ultrasound or radiolabeled)
    - Includes FDA-approved, existing agents already developed but not passed through the FDA approval process, and new agents to be developed through this program.
    - Given the stringent requirements for labeling efficiency, consider cocktails of agents and partnerships between research groups targeting complementary moieties that are expressed across multiple cancer types (e.g., annexin, fibroblast activation protein and CD24), while ensuring that all targets can be probed simultaneously (e.g., are labeled with the same fluorescing moiety).
- Ultrasound or optical microscopy type approaches (Raman, confocal, open top light sheet microscopy, etc.).
- Automated image classification approaches. If classification algorithms exist that will meet the performance metrics with minor modifications, they should be employed, as opposed to developing new algorithms.

Proposers must include on their teams as a co-Investigator at least one (1) oncological surgeon with at least five (5) years of experience in resecting the first cancer type chosen. A user experience/ human factor expert also needs to also be included on the team, as a co-investigator or consultant. Consistent interaction between team members will ensure that the solution will fit in the surgical workflow and could be accepted as a standard of care if the project is successful. In addition, within the first three (3) months of performance, interviews need to be conducted with at least 10 other relevant oncological surgeons performing resections of the first chosen cancer type to ensure a thorough understanding exists of what is considered needed/acceptable in the operating room.

Investigators must also provide the following information in the proposal:
- Intended in vitro assays and animal models to demonstrate efficacy.
- Justification for the number of samples/animals to be used.
- Anticipated risks/pitfalls and alternative solutions.
- Approximate cost estimate for proposed device.
- Cost equation (surgeries saved, costs to the hospital, etc.). An explanation of how the proposed development is expected to be billed/reimbursed (CPT code, insurance pressure, patient pressure, etc.) is also expected.

TA1 metrics (1.3 PROGRAM METRICS) will increase in difficulty and complexity over the course of the PSI program. ARPA-H may request performer data as deemed necessary throughout the program to validate technical progress.

TA2: Critical Structure Localization and Visualization

During interventional procedures, surgeons perform precise mechanical procedures on specific anatomical targets. Many of the tools used, both to perform the procedure and to gain access to the target, are intentionally destructive (scalpels, scissors, etc.); however, surgeons must avoid accidentally damaging critical structures—nerves, blood vessels, ducts, and organs—to prevent long term consequences for the patients' health. Unfortunately, many critical structures have similar color and texture to surrounding tissue and are difficult to see under standard operating room (OR) lighting, with or without magnification. Laparoscopic surgery suffers from a similar lack of visibility, as the standard white lighting and color video imaging used fail to provide the clarity to distinguish relevant anatomy. Furthermore, many critical structures are buried under other soft tissue. In exposing such buried critical structures, surgeons risk cutting, tearing, or otherwise damaging or destroying them.

Currently, surgical procedures can be informed by preoperative 3D imagery. A radiologist performs and may manually annotate cross sections of a Magnetic Resonance Imaging (MRI), computer tomography (CT), or ultrasound, which the surgeon may be able access for reference during surgery. However, the preoperative imagery does not reflect the status during surgery and orientation of the patient, which is especially of concern when working in highly deformable tissue such as breast. In addition, the structures in the preoperative imagery are not necessarily recognizable using the naked eye (or full spectrum laparoscopic video) in the surgical field. The surgeon thus has the burden of mentally performing 3D transformations, image segmentation, and modality fusion while looking back and forth from the preoperative imagery to the patient.

Fluorescent dyes can be used to help identify critical structures in real time during surgery; Indocyanine Green (ICG) may be used during angiography procedures, and methylene blue can be used to visualize parathyroid glands. However, the specificity of these dyes is limited, the depth of the structure is not always clear, and the visualization is not integrated or fused into the surgeon's field of view.

TA2 seeks solutions that impart to the surgeon a real-time, 3D understanding of critical structures in the operating area, thus enabling the clinician to avoid unintentionally damaging critical structures buried under up to 1 cm of other tissue. The solutions must include imaging, visualization, or range-finding components that integrate easily into the surgical workflow. Preference will be given to solutions that identify multiple critical structures and surrounding anatomy; a solution that only focuses on one or two types of critical structure will also be considered, with preference given to nerves and additional structures (e.g., nerves and urethra, or nerve and lymphatics), or nerves alone.

The critical structure location and visualization solution must meet the following requirements:

- The solution must convey 3D understanding to the surgeon such that the surgeon can locate the boundaries of the 3D structure with ±0.5 mm accuracy (up to 2 mm from the surface), ±1 mm (2-5 mm from the surface), and ±2 mm (5-10 mm from the surface)
- Most solutions will include at least two components: one component to extract 3D information from the scene (imaging and algorithm), and one to convey that understanding to the surgeon (registration and visualization).
- The solution must integrate into the surgical workflow without increasing active operating time by more than 10 minutes. It is acceptable to increase the time devoted to collecting preoperative imagery, or to administer contrast agents before surgery.
- The solution must not impede the surgeon's ability to perform the mechanical aspect of surgery. It must be hands-free, integrated onto an already existing surgical tool, or otherwise out of the way. Wearable headsets must include a setting for un-augmented vision or must allow for easy removal. The sterility of the chosen solution must be addressed.
- The initial technology demonstration must be in at least two types of surgeries in which critical structure damage often occurs, such as thoracotomies, mastectomies, prostate cancer removal, or orthopedics.
- The solution must be able to visualize critical structures buried up to 1 cm under other tissue.
- The solution must update its 3D representation in real time with >= 10 frames per second or 10 Hz update rate
- Investigational Device Exemption (IDE) submission
- If applicable, IND submission

To achieve the goals of the program, performers may propose a variety of technical approaches to locate and visualize critical structures during surgery. These approaches can be separate or combined, and may include but are not limited to:

- Fusion of preoperative imagery with real-time intraoperative imagery
- Computational segmentation of imagery, highlighting nerves, blood vessels, and critical organs
- Registration and fusion of infrared imagery with visual spectrum imagery in real time
- Labeling critical structures with contrast agents (oral, intravenous, paint-on or spray-on administration)
- Agent-free imaging of critical structures using autofluorescence, laser speckle contrast imaging, or other techniques
- 3D reconstruction from stereo imaging, point clouds, defocus measurements, or other techniques
- Tool-integrated range finding (e.g., an electrocautery device that measures its distance from nerves and blood vessels)
- Augmented reality (AR) headset visualization
- Integrated laparoscopic video visualization

Proposers must include on their teams as a co-Investigator at least one (1) surgeon with at least five (5) years of experience in performing the type of surgery chosen. A user experience/human

factor expert also needs to also be included on the team, as a co-investigator or consultant. Consistent interaction between team members will ensure that the solution will fit in the surgical workflow and could be accepted as a standard of care if the project is successful. Within the first three (3) months of performance, interviews need to be conducted with at least 10 other relevant surgeons to ensure a thorough understanding exists of what is considered needed/acceptable in the operating room. In addition, a user acceptance metric, defined as the overall percent of yes responses to two (2) questions posed to at least five (5) surgeons, needs to be monitored yearly (starting at the end of year 2) and must be provided in the ARPA-H report - with relevant comments (if any). The two questions will be 'Would you use this solution in your operating room?' and 'Do you feel like this solution improves your ability to see critical structures?'.

The following information also needs to be included in the proposal:

- Design plan for imaging system, if applicable.
- Optimization and validation plan for contrast agent, if applicable.
- Technical plan for imaging algorithms, such as image segmentation, real-time 3D reconstruction from 2D images, 3D transformation and projection of high-resolution preoperative imagery onto low-resolution real-time imagery, or multimodal image registration, if applicable.
- Design plan for surgical tool integration, if applicable.
- Design plan for visualization/display system, if applicable, including an explicit explanation of how the surgeon will perceive depth.
- An explanation of how the team will use principles of user experience and human-centered design to create a product that surgeons are able to and want to use.
- Plans to conduct user experience and human factor analyses.
- Intended tests in phantom tissue, including means to validate accuracy.
- Intended tests in animal models, including means to validate accuracy.
- Anticipated risks and mitigations.
- Cost estimate for the proposed device, including cost equation (complication-related costs avoided, costs to the hospital, etc.). An explanation of how the development is expected to be billed/reimbursed (CPT code, insurance pressure, patient pressure, etc.) is also expected.

TA2 metrics (Section 1.3) will increase in difficulty and complexity over the course of the PSI program. ARPA-H may request performer data as deemed necessary throughout the program to validate technical progress.

1.2.2. Program Structure

The PSI program will be accomplished over two sequential Phases of increasing technical complexity. Decisions to go into Phase II will be determined by the Government based on progress toward achieving Phase I goals. PSI Phases will include programmatic elements to ensure performer success, including a check point between Phases, active and regular US Government stakeholder engagement, equity for disparate patient and market settings for patient/provider buy-

in, and utilization of ARPA-H Project Accelerator Transition Innovation Office (PATIO) assets for commercialization (e.g., Expert/Entrepreneur in Residence (XIR/EIR) meetings).

Within the first three (3) months of the program, ARPA-H will organize a Community Symposium, gathering surgeons and hospital administrators from different socio-economic environments, as well as experts in medical devices and reimbursement approaches. At the minimum, the principal investigator from each team with be required to attend, to better understand how to best design the devices to effectively penetrate the market. This symposium may be immediately preceded by an immersion-based kickoff experience in surgical suites for the relevant procedures addressed by the performers. If possible, this immersion experience will be set in a low-resource or underserved community hospital. In addition, ARPA-H will set up advisory boards tailored to the needs of every project, containing members with regulatory expertise, patent/market analysts, individuals who have transitioned similar development towards the product, and practicing surgeons and pathologists across specialties and practice settings (academic, rural and community hospitals, etc.), as needed. They are meant to ensure a smooth transition of the developments from the lab, through FDA, and to the market. Last, extramural resources and labs will serve as independent verification and validation (IV&V) entities throughout the program, to aid in the iterative development of the planned capabilities and validate findings.

Equity Requirements

ARPA-H and PSI are committed to equitable healthcare access irrespective of race, ethnicity, gender/gender identity, sexual orientation, disability, geography, employment, insurance, and socioeconomic status. To that end, PSI will mandate that each performer agree upon and complete the following actions throughout their time in the program:

- Human surgical samples that will be used to test solutions must be reflective of the patient demographics for the indication studied. Performers will be required to perform adequate research to determine what percentages are appropriate.
- The developments of TA1-A will be tested in two hospitals: Most of the human sample testing will be done at the hospital most convenient for the team. For the last two (2) months of testing, the device must be taken to a rural hospital for validation and reliability testing in the last 10 samples. Should this partnership be difficult to set up prior to the submission of the proposal, ARPA-H will help facilitate the connection during the period of performance.
- Performers must thoughtfully design any solution to be compatible for all potential end users. For example, to accommodate surgeons of differing hand sizes, a handheld device could be adjustable. Performers must explain to ARPA-H how their technologies accommodate a diverse range of end users when they submit their prototypes for review.
- At a minimum, the principal investigator of each team must attend a Community Symposium at the end of Month 3 of the period of performance. The Community Symposium will be organized by ARPA-H and will bring together surgeons, clinicians, medical staff, and hospital administrators from diverse medical facilities in the United

States: (1) Academic medical centers, (2) non-academic community medical centers, and (3) federal government hospitals (e.g., hospitals operated by the Department of Defense, The Department of Human Health and Human Services, or the Veterans Health Administration). The Community Symposium is intended to help performers understand the workflow and cost needs of a diverse range of institutions and clinicians, and to ensure their solutions are broadly applicable and accessible. Performers are encouraged to speak with clinicians and hospital administrators of their own choosing throughout the period of performance. After the symposium, performers should provide a 1-page report of information learned and how the performer will incorporate their learnings into the system design. The report should not detail any confidential information and should be submitted to ARPA-H within four (4) months of starting the project. Only one (1) report is required per performer team, regardless of the number of individuals or institutions the team consists of.

- To prioritize low-cost solutions that can be made more accessible to more end users, the performers must provide a per unit estimated cost analysis of their system that justifies the choice of materials and dimensioning. If a performer chooses a material (e.g., camera, software, computer) that is higher in cost compared to other available materials of the same category, the performer must clearly explain the choice for the higher cost and why a lower cost material is not sufficient. A cost analysis should be provided for the five most expensive items in the system. A preliminary cost analysis should be submitted to ARPA-H within 18 months of funding. A final cost analysis should be submitted before any FDA regulatory filing. Only one set of analyses (primary and final) is required per performer team, regardless of the number of individuals or institutions the team consists of.

Data Sharing Plan

Proposers must agree to openly share deidentified/sanitized data acquired during the period of performance. Any member of the scientific community should have access to the data; registration to a specific repository website is acceptable, but approval needs to be automatic. The specific repository where data will be deposited will be chosen in agreement with the ARPA-H program manager. The proposers will need to present explicit solutions to address the significant data storage and computing challenges presented by the program, with the understanding that the plans and repository may change later in the program.

TA1-A: Phase 1 (24 Months): Proof of concept demonstration

During the 24-month PSI Phase 1, performers will decide whether they will stain the resected tissue. They will perform initial screening and identify the lead compounds, then further optimize these lead compounds. At the same time, they will evaluate potential technologies for in vitro pathology imaging, decide on the lead technology, and develop and optimize the breadboard prototype device that will produce the pathology images.

- Goals of PSI Phase 1 (metrics defined in 1.3 PROGRAM METRICS)

- Identify workflow and components for the entire in vitro pathology automated readout
- If staining agents will be used, begin screening for the appropriate compounds and down-select to three (3) most effective ones each for each cell component to be labeled
- Interview 10 relevant surgeons (by month 3)
- Attend Community Symposium (month 3) and submit report (by month 4)
- Create and submit to ARPA-H initial design history document (by month 12)
- Submit Institutional Review Board (IRB) (and Institutional Animal Care and Use committee (IACUC)) applications (as needed) (by month 12)
- Develop and optimize breadboard device.
- If staining agents will be used, conduct organoid testing (by month 24)
- Prepare prototype for ARPA-H IV&V (by month 23)
- Work with PATIO assets to develop commercialization plan (including an engagement plan with Experts in Residence (EIRs)
- By month 18: Submit Q-submission meeting package and incorporate feedback; establish verification and validation study that would be acceptable for FDA (by month 24)

TA1-A: Phase 2 (36 Months): System integration and validation

During the 36-month PSI Phase 2, performers will validate an end-to-end workflow for in vitro automated intraoperative pathology readout for at least two different cancer types.

- Goals of PSI Phase 2 (metrics defined in 1.3 PROGRAM METRICS)
  - If staining agents will be used, down-select to the single most effective one for each cell component/type to be labeled.
  - Develop, optimize and validate an integrated, automated device for imaging the surface of the specimen or the volume of the resection in cross section.
  - Perform testing in the relevant small animal xenografts and human samples from at least 2 different cancer types.
  - Expected performance: 10 min/surgical sample (with an additional 5 min allowed for sample preparation), which can be as large as 10 cm x 10 cm x 10 cm (or the equivalent spherical volume) (by month 60)
  - Sensitivity should be ≥98% and specificity ≥95%, demonstrated in surgical specimens from >150 human surgeries, for each of the cancer types selected. The ground truth of the pathological read should be set by three pathologists using Formalin-Fixed Paraffin-Embedded (FFPE). (by month 60)
  - If the metrics/number of subjects above are not meaningful for a particular case, proposing teams are expected to provide their own metrics and describe the quantitative improvement those metrics represent over the state-of-the-art. Power analysis calculations are needed to support the proposed metrics.
  - Work with PATIO assets for right-to-practice analysis, patent application, patent landscape analysis, business case, contract research organization (CRO) identification
  - Next step funding/pathway identified (by month 48)

- 510k/PMA/de Novo FDA application (by month 54)

TA1-B: Phase 1 (24 Months): Proof of concept demonstration

During the 24-month PSI Phase 1, performers will decide whether they will use contrast agents for *in vivo* tissue labeling. They will perform initial screening and identify the lead compounds, then further optimize these lead compounds. At the same time, they will evaluate potential technologies for in vivo pathology imaging, decide on the lead technology, develop and optimize the breadboard prototype device that will produce the in vivo pathology images.

- Goals of PSI Phase 1 (metrics defined in Section 1.3)
    - Identify workflow and components for the entire in vivo pathology automated readout
    - Interview 10 relevant surgeons (by month 3)
    - Attend Community Symposium (month 3) and submit report (by month 4)
    - Create and submit to ARPA-H initial design history document (by month 12)
    - Submit IACUC application (by month 12)
    - If contrast agents will be used:
        - Begin screening for the appropriate compounds and down-select to 3 most effective ones; demonstrate labeling of 70% of relevant cancer types, with a Go/No Go decision on the compound (by month 24)
        - Conduct INTERACT meeting w/ FDA; finalize verification and validation plan needed for FDA Investigational New Drug (IND) submission. (by month 18)
        - Conduct basic in vitro/in vivo pharmacology/toxicity tests for the 3 lead compounds with a Go/No Go Decision (for each compound) by month 24. A single, 100x dose intended to be used in humans will be used (scaled by the ratio of body weights). These tests will include:
            - In vitro human ether-a-go-go-related gene (hERG) tests indicating no cardiotoxicity
            - Functional observational battery according to (40 CFR § 798.6050) indicating no neurotoxicity
            - A liver panel (including, at the minimum, alanine transaminase and aspartate transaminase) indicating no liver toxicity
        - With aid from PATIO, identify potential GLP and cGMP manufacturing partners, as well as CROs that will perform toxicity, biodistribution, stability studies
    - ROI identification means finalized (by month 24)
    - Complete breadboard device; Site preparation time and region of interest (ROI) imaging time: 30min/ROI (by month 24)
    - Submit Q-submission meeting package and incorporate feedback(by month 15)
    - Establish verification and validation study (by month 24)
    - Work with PATIO assets to develop commercialization plan (including an engagement plan with XIR/EIRs)
    - Prepare prototype for ARPA-H IV&V (by month 23)

TA1-B: Phase 2 (36 Months): System integration and validation

During the 36-month PSI Phase 2, performers will develop an end-to-end workflow for in vivo automated intraoperative pathology readout and test it in at least two different cancer types in two relevant animal models of disease (one rodent and one large animal model)

- Goals of PSI Phase 2 (metrics defined in 1.3 PROGRAM METRICS)
    - Use PATIO assets for right-to-practice analysis, submit patent application, patent landscape analysis, business case, CRO identification (by month 36)
    - Submit Pre-IDE meeting package and incorporate feedback (by month 36)
    - If macroscopic cancer labeling agents are part of the foreseen integrated workflow
        - Having met all criteria of PSI Phase 1, contrast agents must demonstrate 90% cancer labeling in a large animal model with a Go/No Go determination (by month 42)
        - Submit Pre-IND meeting package and incorporate feedback (by month 36)
        - Secure contract with established partner for producing GLP/cGMP contrast agents and produce agent for 20-100 patients (by month 36)
        - Secure contract with established partner for toxicity and biodistribution/ 2 animal models and complete studies. The toxicity/biodistributions studies agreed to with FDA in prior meetings will be carried out (by month 48).
        - Secure contract for contrast agent stability studies and complete studies (by month 51)
        - Submit IND application (by month 54)
    - Complete integrated device; region of interest (ROI) imaging time: 10 min/ROI (by month 48)
    - Finalize optimization of classification algorithm; ≥98% sensitivity and ≥95% specificity, measured against ground truth set by one pathologist reading FFPE (by month 54)
    - Submit IDE application (by month 54)
    - Imaging time: 3 min/ROI or 10 min/entire cavity (with an additional 5 minutes allowed for cavity preparation) (by month 60)

Note: if performers develop a new contrast agent, this agent will undergo regulatory evaluation alone, not in conjunction with the device/software combination.

TA2 Phase 1 (24 Months): Proof of concept demonstration

During the 24-month PSI Phase 1, TA2 performers will develop a prototype device that localizes critical structures and conveys the 3D information to the surgeon. This device should achieve Technology Readiness Level (TRL) 4-5, defined as: subsystems validation and demonstration in a laboratory environment. They will demonstrate the device in phantom tissue, and show that the imaging technology, image processing algorithms, and visualization subsystems work in concert. If a new contrast agent is developed, they will identify and optimize lead compounds.

Goals of PSI TA2 Phase 1 (metrics defined in 1.3 PROGRAM METRICS)

- Create prototype subsystems for imaging, image processing, and visualization
- Demonstrate location and visualization of critical structures in TRL 4-5 device using tissue phantom
- Create initial design history document (by month 12)
- Interview 10 relevant surgeons (by month 3)
- Attend Community Symposium (month 3) and submit report (by month 4)
- Submit patent applications (by month 18)
- Submit IRB (and IACUC) applications (as needed) (by month 12)
- If developing new contrast agents:
    - Screen for appropriate compounds and down-select to three (3) most effective ones.
    - Conduct INTERACT meeting w/ FDA; finalize verification and validation plan needed for FDA submission. (by month 18)
    - With aid from PATIO, identify potential good laboratory practice (GLP) (if applicable) and current good manufacturing practice (cGMP) manufacturing partners, as well as CROs that will perform toxicity, biodistribution, stability studies.
    - Conduct basic in vitro/in vivo pharmacology/toxicity tests for the 3 lead compounds with a Go/No Go Decision (by month 24). A single, 100x dose intended to be used in humans will be used (scaled by the ratio of body weights). These tests will include:
        - In vitro human ether-a-go-go-related gene (hERG) tests indicating no cardiotoxicity
        - Functional observational battery according to (40 CFR § 798.6050) indicating no neurotoxicity
        - A liver panel (including, at the minimum, alanine transaminase and aspartate transaminase) indicating no liver toxicity
- For all devices:
    - Submit Q-submission meeting package and incorporate feedback (by month 18)
    - Establish verification and validation study (by month 24)
    - Prepare prototype for ARPA-H IV&V (by month 23)
    - Work with ARPA-H to develop regulatory strategy based on FDA feedback (by month 24)
    - With aid from PATIO, identify potential CROs that will productize the device (by month 24)

TA2: Phase 2 (36 Months): System integration, optimization, and validation

During the 36-month PSI Phase 2, performers will develop a device that locates critical structures and conveys that 3D information to the surgeon. This device should achieve TRL 6-7: successful integrated system demonstration in a relevant environment with testing to validate system design specifications. All subsystems should be fully integrated, and the size and shape of the device should reflect that of the final commercial product. Performers will demonstrate the device in a large animal model and will have fulfilled FDA requirements to receive device approval for clinical trials.

Goals of PSI TA2 Phase 2 (metrics defined in 1.3 PROGRAM METRICS)

- Create device prototype with integrated subsystems (by month 54)
- Demonstrate location and visualization of critical structures in large animal surgery (by month 54)
- Characterize performance gain of procedure performed with the device compared to unaided (by month 60)
- Conduct user experience and human factors analysis evaluating surgeons' ease of use and increased anatomical awareness (by month 54)
- Document device design specifications (by month 54)
- Continuously update design history document
- Secure partner for cGMP device manufacture (by month 48)
- Submit Pre-IDE meeting package and incorporate feedback (by month 36)
- Complete all IDE-enabling studies and submit IDE application (by month 54)

If developing a contrast agent:

- Submit Pre-IND meeting package and incorporate feedback (by month 36)
- Secure contract with established partner for producing GLP/cGMP contrast agents and produce agent for 20-100 patients (by month 36)
- Secure contract with established partner for toxicity and biodistribution/ 2 animal models and complete studies. The toxicity/biodistributions studies agreed to with FDA in prior meetings will be carried out (by month 48)
- Secure contract for contrast agent stability studies and complete studies (by month 48)
- Submit IND application (by month 54)

A summary of the program layout and minimum milestones is presented below. If performers start in a more advanced state, these milestones will need to be adjusted accordingly (and be thoroughly detailed in the proposal).

	TA1-A: Phase I (24 months)							
	Proof of concept demonstration							
	Year 1				**Year 2**			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Staining dye	Initial target screening		Normal and homogeneous organoid testing		Dye optimization		Heterogeneous organoid testing	
Device	Technology drill-down		Breadboard device development		Optimization of breadboard device			
Digital Pathology					Data pipeline development			
Milestones	- IACUC submission - Breadboard device completion, create initial design history document -Attend Community Symposium, submit report; interview 10 relevant surgeons - Normal organoid and homogeneous cancer organoid testing - Sample preparation and image generation time: 20min/slice				- IRB submission - Q-submission completion, incorporate feedback, develop verification and validation plan - ARPA-H IV&V of prototype - Heterogeneous cancer organoid testing - Sample preparation and image generation time: 10min/slice or 60 min/10 slices			

	TA1-A: Phase II (36 months)											
	System integration and validation											
	Year 3				Year 4				Year 5			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Staining dye	Animal xenograft agent testing		Human sample testing				Automated human sample testing		System integration and optimization, automated human sample testing		System validation	
Device	Integrated device development		Device automation									
Digital Pathology	Classification algorithm development						Classification algorithm optimization					
Milestones	- Sample preparation+ image generation/classification time: 5min/slice or 50 min/10 slices - 80% concordance between MANUAL intraoperative pathology and FFPE (3 readers, 2 cancer types) - Right-to-practice analysis, patent application, patent landscape analysis, business case, CRO identification				- Sample preparation + image generation/ classification time: 30 min/10 slices - ≥90% sensitivity and ≥90% specificity between AUTOMATED intraoperative pathology in 2 cancer types (ground truth=3 pathologists' read of FFPE) - Next step funding/pathway identified				- Sample preparation: 5 min, image generation/classification time 10 min/surgical sample - ≥98% sensitivity and ≥95% specificity of AUTOMATED intraoperative pathology in 2 cancer types (ground truth=3 pathologists' read of FFPE) - 510k/PMA/De Novo FDA submission			

	TA1-B: Phase I (24 months)							
	Proof of concept demonstration							
	Year 1				Year 2			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Contrast Agent	Initial agent screening		Target candidate identification		Agent optimization		Xenograft+ small animal testing	
Device	Technology drill-down		Breadboard device development		Optimization of breadboard device			
Digital Pathology					Data pipeline development			
Milestones	- Labeling in 50% of relevant cancer types/subtypes - IACUC submission - Attend Community Symposium, submit report; interview 10 relevant surgeons - Breadboard device completion - Site preparation time and ROI imaging time: 40min/ROI (2cm x 2cm)				- Labeling in 70% of relevant cancer types/subtypes - ROI identification means finalized - Initial toxicology studies - INTERACT meeting w/ FDA; verification and validation plan finalized - ARPA-H IV&V of prototype - Site preparation time and ROI imaging time: 30min/ROI (2cm x 2cm)			

<table>
<tr><td></td><td colspan="12">TA1B: Phase II (36 months)</td></tr>
<tr><td></td><td colspan="12">System integration and validation</td></tr>
<tr><td></td><td colspan="4">Year 3</td><td colspan="4">Year 4</td><td colspan="4">Year 5</td></tr>
<tr><td></td><td>Q1</td><td>Q2</td><td>Q3</td><td>Q4</td><td>Q1</td><td>Q2</td><td>Q3</td><td>Q4</td><td>Q1</td><td>Q2</td><td>Q3</td><td>Q4</td></tr>
<tr><td>Contrast Agent</td><td colspan="4">Xenograft + small animal testing</td><td colspan="2">Large animal testing</td><td colspan="2" rowspan="2">Large animal testing</td><td colspan="2" rowspan="3">System integration and optimization, large animal testing</td><td colspan="2" rowspan="3">System validation</td></tr>
<tr><td>Device</td><td colspan="2">Integrated device development</td><td colspan="6">Device automation</td></tr>
<tr><td>Digital Pathology</td><td colspan="6">Classification algorithm development</td><td colspan="2">Classification algorithm optimization</td></tr>
<tr><td>Milestones</td><td colspan="4">- Site preparation time and ROI imaging time: 20min/ROI (2cm x 2cm);
- labeling of 90% of relevant cancer types (first cancer)
- 80% concordance between MANUAL intraoperative pathology and FFPE (1 reader, 2 cancer types)
- Right-to-practice analysis, submit patent application, patent landscape analysis, business case, CRO identification, pre-IND, pre-IDE meetings w/ FDA
- GLP/GMP contrast agent synthesis</td><td colspan="4">- Site preparation time and ROI imaging time: 10min/ROI (2cm x 2cm)- if deterministically selected, otherwise 30 min for entire resection site
- labeling of 70% of second cancer
- ≥90% sensitivity and ≥90% specificity between AUTOMATED intraoperative pathology in 2 cancer types (ground truth=1 pathologist's read of FFPE)
- Next step funding/pathway identified
- Toxicology, biodistribution and stability tests completed</td><td colspan="4">- Site preparation time 5min + and ROI imaging/classification time: 3 min/ROI (2cm x 2cm)- if deterministically selected, otherwise 10 min for entire resection site
- ≥98% sensitivity and ≥95% specificity of AUTOMATED intraoperative pathology in 2 cancer types (ground truth=1 pathologist' read of FFPE)
- IND and IDE submission</td></tr>
</table>

<table>
<tr><td rowspan="3"></td><td colspan="8">TA2: Phase I (24 months)</td></tr>
<tr><td colspan="8">Proof of concept demonstration</td></tr>
<tr><td colspan="4">Year 1</td><td colspan="4">Year 2</td></tr>
<tr><td>Q1</td><td>Q2</td><td>Q3</td><td>Q4</td><td>Q1</td><td>Q2</td><td>Q3</td><td>Q4</td></tr>
<tr><td>Agent</td><td colspan="2">Initial agent screening</td><td colspan="2">Target candidate identification</td><td colspan="2">Agent optimization</td><td colspan="2">Small animal model testing</td></tr>
<tr><td>Device</td><td colspan="2">Technology drill-down</td><td colspan="2">Breadboard device development</td><td colspan="2">Optimization of breadboard device</td><td colspan="2">Testing on phantom tissues</td></tr>
<tr><td>Algorithm</td><td colspan="2"></td><td colspan="4">Initial algorithm development</td><td colspan="2">Algorithm testing on phantom tissue data</td></tr>
<tr><td>Milestones</td><td colspan="4">-Initial design history document
-Attend Community Symposium, interview 10 relevant surgeons, submit report;
-IACUC submission and approval</td><td colspan="4">- Sense buried critical structure at up to 0.5 cm depth
- Real-time update rate >=0.5 Hz
- Accuracy (surgeon estimate of distance from structure) <=3mm
- Q-submission to FDA; create verification and validation plan
- Initial toxicology studies
- (if applicable) INTERACT meeting w/ FDA; verification and validation plan finalized
- ARPA-H IV&V of prototype
- User acceptance >=60%</td></tr>
</table>

<table>
<tr><td rowspan="3"></td><td colspan="12">Phase II (36 months)</td></tr>
<tr><td colspan="12">System integration and validation</td></tr>
<tr><td colspan="4">Year 3</td><td colspan="4">Year 4</td><td colspan="4">Year 5</td></tr>
<tr><td></td><td>Q1</td><td>Q2</td><td>Q3</td><td>Q4</td><td>Q1</td><td>Q2</td><td>Q3</td><td>Q4</td><td>Q1</td><td>Q2</td><td>Q3</td><td>Q4</td></tr>
<tr><td>Agent</td><td colspan="4">Small animal model testing</td><td colspan="4">Large animal model testing</td><td colspan="2" rowspan="3">System integration and optimization</td><td colspan="2" rowspan="3">System validation</td></tr>
<tr><td>Device</td><td colspan="4">Integrated device development</td><td colspan="4">Device testing in animals</td></tr>
<tr><td>Algorithm</td><td colspan="4">Algorithm refinement</td><td colspan="2">Algorithm optimization</td><td colspan="2">Algorithm validation on large animal data</td></tr>
<tr><td>Milestones</td><td colspan="4">- Sense burried structure up to 1cm deep
- Real time update rate>=2Hz
- Accuracy ±2 mm
- pre-IDE and (if applicable) pre-IND meetings w/ FDA
-Submit patent application(s)
-Identify CRO
- (if applicable) GLP/GMP synthesis of contrast agent
-Right-to-practice analysis, patent landscape analysis, business case
- User acceptance >=70%</td><td colspan="4">-Sense buried critical structure at up to 1cm depth
- Real-time update rate >=5 Hz
- Accuracy (surgeon estimate of distance from structure) ±1 mm (up to 2 mm from the surface), ±2 mm (2-5 mm from the surface)
- User acceptance >=80%
- Toxicity, biodistribution and stability tests completed
- Next steps/funding pathway identified</td><td colspan="4">-Sense buried critical structure at up to 1 cm depth
-Real-time update rate >=10 Hz
-Accuracy (surgeon estimate of distance from structure) ±0.5 mm (up to 2 mm from the surface), ±1 mm (2-5 mm from the surface), and ±2 mm (5-10 mm from the surface)
-90% decrease in inadvertent critical structure damage compared to unaided case
-User acceptance >=90%
-Design history document
-Submit IDE and (if applicable) IND application</td></tr>
</table>

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 minimum 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. If the metrics/number of subjects below are not meaningful for a particular case, proposing teams are expected to provide their own metrics and describe the quantitative improvement those metrics represent over the state-of-the-art. Power analysis calculations are needed to support the proposed metrics.

TA1-A Metrics and Objectives

The overall program goals for TA1-A are listed in Table 1. The expected metrics per phase in TA1-A 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 PSI Phase.

Table 1. TA1-A Overall Program Goals

Intended scope of development	Automated bedside pathology analysis of oncological samples for margin analysis
Allowed in vivo contrast agent	No
Allowed in vitro staining of resected specimen	Yes
Allowed freezing of resected specimen	No
Intended target	The solution chosen must be generally applicable and demonstrated in two cancer types. For the first cancer, breast, colorectal, head and neck or ovarian cancers should be selected (with the listing order above defining preference order). Any cancer type can be selected for the second validation case.
Solution must accommodate (and image) specimen of size	10 cm x 10 cm x 10 cm or equivalent spherical volume
Imaging resolution	0.5 µm. A multiscale approach, in which the majority of the sample is imaged at 1-2 µm, while regions deemed suspicious by the low resolution pass-through are imaged at 0.5 µm, will also be considered acceptable.
Imaging and analysis time for entire specimen	10 min, with 5 additional minutes allowed for sample preparation
Imaging type	Surface or cross section. If specimen is grossed, slices will be obtained at intervals no more than 4 mm apart. If the surface of the sample is imaged, imaging of the entire surface is desired.
Target human surgical samples to be evaluated for workflow validation (per cancer type)	150
Sensitivity and specificity (for each cancer type)	≥98% sensitivity; ≥95% specificity
Final positive margin rate*	<2%
*This refers to the unknown margin rate. In some cases, the surgeon may be informed that the margin remained positive, but decided to still finalize surgery, as further resection would incapacitate the patient. Such cases would count towards success, not failure modes for the integrated solution developed.	

Table 2. TA1-A Metrics for Each Phase

Metrics	**Specifications**
Phase 1 (Proof of concept demonstration)	

Staining agents	If used, down-select to 3 most effective ones each for each cell component to be labeled
Image field of view	4 cm x 4 cm x 4 cm or equivalent spherical volume
Imaging resolution	10 µm
Imaging type	Entire specimen surface imaging is preferred; if sample grossing is chosen instead, it must provide margin information no sparser than one slice every 4 mm over the volume of the sample (e.g., for a sample of 4 cm on the longest axis, it must be able to image 10 slices).
Imaging time	Sample preparation and image generation time: 10 min/slice or 60 min/10 slices
Documentation Requirement	Design history document
Additional Requirement(s):	• By month 18: Submit Q-submission meeting package and incorporate feedback. • Interview 10 relevant surgeons (by month 3) • Attend Community Symposium (month 3) and submit report (by month 4) • Work with ARPA-H PATIO to develop commercialization plan • With aid from PATIO, identify CROs that will productize device. • Submit IRB (and IACUC) applications (as needed) • Prepare prototype for ARPA-H IV&V
Phase 2 (System integration and validation)	
Staining agents	If used, downselect to a single one for each cell component to be labeled
Image field of view	10 cm x 10 cm x 10 cm
Imaging resolution	0.5 µm. A multiscale approach, in which the majority of the sample is imaged at 1-2 µm, while regions deemed suspicious by the low resolution pass-through are imaged at 0.5 µm, will also be considered acceptable.
Imaging type	Entire specimen surface imaging is preferred; if sample grossing is chosen instead, it must provide margin information no sparser than one slice every 4 mm over the volume of the sample (e.g., for a sample of 10 cm on the longest axis, it must be able to image 25 slices).
Imaging time	Sample preparation: 5 min, and image generation time: 10 min per specimen
Outcome	≥98% sensitivity and ≥95% specificity, measured against ground truth set by 3 pathologists reading FFPE in 100 relevant human surgical samples, for each of the cancer type selected (by month 54)
Usability	90% reduction in positive margin rate
Safety	N/A
Manufacturing Standards	Device manufactured by identified CRO

Documentation Requirement	Design history document
Additional Requirement(s):	• Use PATIO assets for right-to-practice analysis, patent application, patent landscape analysis, business case. • 510k/PMA/De Novo FDA submission (by month 54)

TA1-B Metrics and Objectives

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

Table 3. TA1-B Overall Program Goals

Intended scope of development	Automated in vivo pathology analysis of resection cavity following cancer removal
Allowed in vivo contrast agent	Yes
Intended target	The solution chosen must be generally applicable and demonstrated in two cancer types. For the first cancer, prostate, breast or ovarian cancers should be selected (with the listing order above defining preference order). Any cancer type can be selected for the second validation case.
Imaging field of view (FOV)	Entire resection site. Alternatively, reduction of the field of view (FOV) to <4 regions of interest (ROIs) can be performed through deterministic means (e.g., in vivo agent highlighting minimal patches of tissue). Assessment of surgeon as to what margin may be positive is not considered acceptable. ROIs must be reduced to no larger than 2 cm x 2 cm, or the equivalent circular surface area.
Imaging and analysis time	10 min for entire resection site, with 5 additional minutes allowed for cavity preparation. Alternatively, 3 min/ROI with size up to 2 cm x 2 cm, with 5 min total allowed for cavity preparation
Imaging resolution	0.5 μm
Imaging type	Surface
Validation	2 relevant animal models (one rodent, one larger)
Sensitivity and specificity (for each cancer type)	≥98% sensitivity and ≥95% specificity
Final positive margin rate*	<2%
*This refers to the unknown margin rate. In some cases, the surgeon may know that the margin remained positive, but decided to still finalize surgery, as further resection would incapacitate the patient. Such cases would not count towards failure modes for the integrated solution developed.	

Table 4. TA1-B Metrics for Each Phase

Metrics	**Specifications**
Phase 1 (Proof of concept demonstration)	

Contrast agents	If used, down-select to 3 most effective ones each for the cancer type considered
Contrast agent specificity	Label 70% of relevant cancer studied (e.g., label 70% all prostate cancer types or subtypes expected to be seen in vivo)
Image field of view	2 cm x 2 cm x 2 cm (or the equivalent circular surface area)
Imaging resolution	**10 um**
Imaging type	Resection cavity surface imaging
Imaging time	Site preparation and imaging time in vivo: 30 min for a 2 cm x 2 cm ROI (or the equivalent circular surface area)
Documentation Requirement	Design history document
Additional Requirement(s):	• ROI identification means finalized • Interview 10 relevant surgeons (by month 3) • Attend Community Symposium (month 3) and submit report (by month 4) • INTERACT meeting w/ FDA; verification and validation plan finalized • Submit IACUC applications/ obtain approvals • Pass basic, single dose pharmacology/toxicity tests at 100x intended dose if contrast agents are used • Prepare prototype for ARPA-H IV&V
Phase 2 (System integration and validation)	
Contrast agents	If used, down-select to the single most effective for the cancer type considered
Contrast agent specificity	Label 90% of relevant cancer studied in relevant animal models (e.g., label 90% all prostate cancer types or subtypes expected to be seen in vivo) and 70% of the second cancer type selected
Image field of view	2 cm x 2 cm x 2 cm (or the equivalent circular area) if using deterministic means to select ROIs to be imaged; otherwise, entire resection cavity
Imaging resolution	**0.5 um**
Imaging type	Resection cavity surface imaging
Imaging time	Site preparation and imaging time in vivo: 3 min for a 2 cm x 2 cm ROI selected through deterministic means (which does not include surgeon's opinion as to what part may be positive), or 10 min total cavity imaging (plus 5 min cavity preparation)
Outcome	≥98% specificity and ≥95% sensitivity, measured against ground truth set by 1 pathologist reading FFPE
Usability	90% reduction in positive margin rate
Safety	N/A
Manufacturing Standards	• Device manufactured by identified CRO • GLP/GMP synthesis for contrast agent • Toxicity, biodistribution and stability tests completed

Documentation Requirement	Design history document
Additional Requirement(s):	• If prostate cancer is chosen, integrate device with standard-of-care surgical robot • Right-to-practice analysis, submit patent application, patent landscape analysis, business case, CRO identification, pre-IND, pre-IDE meetings w/ FDA (by month 36) • Toxicity, biodistribution and long-term stability tests completed (by month 36) • IND and IDE submission (by month 54)

TA2 Metrics and Objectives

The overall program goals for TA2 are listed in Table 5. The expected metrics per phase in TA2 are listed in Table 6.

Table 5. TA2 overall program goals

Intended scope of development	Real time location and visualization of critical structures during surgery
Allowed in vivo contrast agent	Yes
Intended target	Nerves, blood vessels, lymphatics, parathyroid glands, ureter, bile ducts, and other structures commonly damaged in surgery due to lack of clear visualization. Preference will be given to solutions that detect multiple critical structures and surrounding anatomy, followed by detection of nerves and additional structures (e.g., nerves and urethra, or nerves and lymphatics), followed by detection of nerves alone.
Imaging field of view (FOV)	Surgical working area, no smaller than 3x3 cm or equivalent circular area
Imaging and analysis time	Intraoperative visualization must occur in real time with a refresh rate of >= 10 frames per second. Preoperative imaging, image processing, and image annotation is allowed.
Imaging modalities allowed	Visual spectrum, infrared, MRI, CT, X-ray, positron emission tomography (PET), ultrasound, and others
Validation	• Demonstration in surgery on relevant large animal model • Identification of structures with device compared to without the device • Validation and verification as specified by FDA experts in pre-IDE and (if applicable) pre-IND submission • Evaluation by ARPA-H specified IV&V
Outcome	• Outcome comparison: critical structure damage with and without the device in animal models

	• Surgical experience: surgeon confidence and ease of use, measured by user experience and human factors evaluation

Table 6. TA2 metrics for each phase

Metrics	Specifications
Phase 1 (Proof of concept demonstration)	
Depth of buried critical structure	Up to 0.5 cm
Real-time update rate	0.5 Hz
Accuracy (surgeon estimate of distance from surgical tool to critical structure)	±3 mm accuracy (up to 2 mm from the surface), ±5 mm (2-5 mm from the surface), and ±8 mm (5-10 mm from the surface)
Documentation Requirement	Design history document
Additional Requirement(s):	• Submit Q-submission meeting package and incorporate feedback (by month 18); establish verification and validation study (by month 24) • (if applicable) Conduct INTERACT meeting w/ FDA; finalize verification and validation plan needed for IND submission (by month 18) • Work with ARPA-H PATIO to develop regulatory strategy based on FDA feedback. • Interview 10 relevant surgeons (by month 3) • Attend Community Symposium (month 3) and submit report (by month 4) • With aid from PATIO, identify potential GLP (if applicable) and cGMP manufacturing partners, as well as CROs that will perform toxicity, biodistribution, stability studies (if applicable) • Pass basic, single dose pharmacology/toxicity tests at 100x intended dose if contrast agents are used • Prepare prototype for ARPA-H IV&V
Phase 2 (System integration, optimization, and validation)	
Depth of buried critical structure	Up to 1 cm
Real-time update rate	10 Hz
Accuracy (surgeon estimate of distance from surgical tool to critical structure)	±0.5 mm accuracy (up to 2 mm from the surface), ±1 mm (2-5 mm from the surface), and ±2 mm (5-10 mm from the surface)
Outcome	90% decrease in inadvertent critical structure damage compared to unaided case
Usability	Human factors analysis evaluating surgeons' ease of use

	User acceptance metric: percent of total 'yes' responses from at least 5 surgeons answering the questions 'Would you use this solution in your operating room?' and 'Do you feel like this solution improves your ability to see critical structures?'
Safety	Complete all IDE-enabling studies and submit IDE application. Complete all IND-enabling studies and submit IND application (if applicable)
Manufacturing Standards	cGMP-compliant manufacturing plan in place, partner secured, agent synthesized for 20-100 patients (if applicable)
Documentation Requirement	Design history document
Additional Requirement(s):	Use PATIO assets to develop commercialization plan, secure IP, streamline regulatory pathway (FDA consultants), scale manufacturing capabilities, etc.

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 TA1-A, TA1-B or TA2. 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. A group (e.g., a contrast agent or digital pathology developer) may participate in two proposals but cannot be the *prime* proposer on both. Proposals may only address TA1-A, TA1-B, or TA2, with the single exception of a combined response to TA1-B and TA2 in which a significant component of the technical solution (e.g., microscopy method or contrast agent) addresses both Technical Areas.

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

2. Award Information

2.1 GENERAL AWARD INFORMATION

[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).

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 OTs). 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 OTs.

In all cases, the Government's applicable OT 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.

3. Eligibility Information

3.1.ELIGIBLE APPLICANTS

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

3.1.1. Federal Entities and Federally Sponsored Entities

Federal entities and federally sponsored entities (e.g., Government/National laboratories, Federally Funded Research and Development Centers (FFRDC), University Affiliated Research Center (UARC), military educational institutions, etc.) are not eligible for award under this announcement. However, ARPA-H is committed to working with its federal partners. Federal partners interested in working with ARPA-H on this program should contact PSI@arpa-h.gov to discuss supporting this effort.

3.1.2. Other Applicants

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

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 and regulations 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 submit an OCI mitigation plan that identifies and discloses all facts relevant to potential OCIs involving the proposer's organization and any proposed team member (proposed sub-awardee). Although the FAR does not apply to OTs, 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 Science, Engineering, and Technical Assistance 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 sub-awardee) 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.

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 (Arial or Times New Roman) and 1-inch margins. 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 four (4) pages in length. The maximum page count excludes the cover page and the Rough Order of Magnitude. The Government will not review pages beyond 4; and any abstract submitted that exceeds four (4) 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 (1) or two (2) 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. The list of citations does not count towards the page limit. 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. Cost sharing is neither required nor forbidden as well as not considered a factor in evaluation. The below table may be used for this breakdown:

Cost Category	**Amount**
Direct Labor	
Indirect Costs	
Sub-awardees	
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 2 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, font size should be no less than 12 pt (Arial or Times New Roman), and page numbers should be included at the bottom of each page. Copies of all documents submitted must be clearly labeled with the ARPA-H BAA number, proposer organization, and proposal title/proposal short title (in the header of each page). Please use the following Title Format: "Volume I_Lead Org", "Volume II_Lead Org", "Supporting Document_Lead Org". The maximum page count for Volume 1 is thirty (30) pages. This includes sections A-E described below (Executive Summary, Goals and Impact, Technical Plan, Management Plan and Capabilities). Sections F-I below are not included in the page count (Statement of Work (SOW), Schedule and Milestones, Technology Transfer Plan, and References). However, for all sections, ARPA-H encourages conciseness to the maximum extent practicable. No other supporting materials may be submitted for review. Volume I should include the following components:

A. Volume I, Technical and Management Proposal

Section I: Administrative

Cover Page

1. BAA number (75N99223R0004);
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;**~~
8. Technical point of contact (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, email; and
10. Total funds requested from ARPA-H, and the amount of cost share (if any).

Section II: 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. Provide an overview of the current and previous research and development (R&D) efforts related to the proposed research and identify any challenges associated with such efforts, including any scientific or technical barriers encountered in the course of such efforts or challenges in securing sources of funding, as applicable. Describe the innovative aspects of the project in the context of existing capabilities and approaches, clearly

delineating the uniqueness and benefits of this project in the context of the state of the art, alternative approaches, and other projects from the past and present. Describe how the proposed project is revolutionary and how it significantly rises above the current state-of-the-art. Describe the deliverables associated with the proposed project 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 sub-awardees, 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 OT/Grant Officer's Representative equivalent for each award instrument (e.g., Grants Management Specialist), coordinate the effort across co-performer, vendor, and sub-awardee 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/sub-awardees of the proposed effort. Include risk management approaches. Describe any formal teaming agreements required to execute this program.

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

F. Statement of Work (SOW): 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. The SOW will not pe part of the technical evaluation.

For each task/subtask, provide:

- A detailed description of the approach to be taken to accomplish each defined task/subtask.
- Identification of the primary organization responsible for task execution (prime awardee, sub-awardee(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.

I. References: Add a list with the cited literature

B. Volume II, Cost Proposal

(1) All proposers must submit the following:

Cover Page

1. BAA number (75N99223R0004);
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 OT;
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 provided MS Excel ARPA-H Standard Cost Proposal Spreadsheet in the development of cost proposals[4]. 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 sub-awardees. In addition to using the cost proposal spreadsheet, the cost proposal still must include all other items required in this announcement that are not covered by the editable spreadsheet. Sub-awardee cost proposal spreadsheets may be submitted directly to the Government by the proposed sub-awardee via email to the address in the Part I *Overview Information*.

The proposers should also provide the Forward Price Rate Agreement (FPRA) letter.

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.

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; sub-agreements; travel; materials; other direct costs; overhead charges, etc.). For materials exceeding $5,000, a backup (screenshot, quote, etc) is required. For indirect costs, if one has been negotiated with the federal government, please provide the most current

[4] Proposers and any subproposers requesting a cooperative agreement do not need to use the Standard Cost Proposal Spreadsheet. Instead, cooperative agreement applicants must the MS Excel SF-424A Budget Worksheet Research provided via https://www.grants.gov.

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

indirect cost agreement (e.g., Colleges and Universities Rate Agreement, Forward Pricing Agreement, Provisional Billing Rates, etc.). The contractor must provide the point of contact (email and phone number) for the rate agreements (FPRA or Provisional Billing rates).

   b. Further broken down by task and phase

2. **Major Program Tasks by Fiscal Year**
3. **An Itemization of Major Sub-agreements**
   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**
   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.

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, please provide screenshots/quotes. For indirect costs, if available, please provide the most current indirect cost agreement (e.g., Colleges and Universities Rate Agreement, Forward Pricing Agreement, Provisional Billing Rates, etc.).

Sub-awardee Proposals

The awardee is responsible for compiling and providing all sub-awardee proposals for the Grants or OT Officer as applicable. Sub-awardee 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. A cost workbook is required for ALL sub-awardees.

All proprietary sub-awardee 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

The government will protect any submissions marked as proprietary. 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. Proposers must also submit the Vertebrate Animals Section (VAS) as required by the NIH Office of Laboratory Animals Welfare. See here for requirements for the VAS: https://olaw.nih.gov/guidance/vertebrate-animal-section.htm).

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 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 OTs.

Intellectual Property

[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

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 OT 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 a proposal. Entities that are not currently registered in SAM are advised that the process can take time and are encouraged to begin the registration process as soon as possible. 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.

This BAA is open and in effect until the BAA Closing Date outlined in Part I., Overview Information of this BAA.

Full proposals requesting OTs must also be received electronically to eCPS (https://ecps.nih.gov) by the due dates outlined in Part I, *Overview Information* of this BAA.

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

Abstract Submission

Refer to Section 6.1.1. for how ARPA-H will notify proposers to submit a full proposal.

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 Other Transaction Agreements

Proposers requesting an OT must provide a document describing Current and Pending Support. The document is mandatory for all Senior/Key Personnel including the PD/PI. This document 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.

The document may be included in the Cost Proposal volume.

(2) 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 (3) 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

Pre-award costs will **not** be reimbursed unless a pre-award cost agreement is negotiated prior to the award.

4.4. QUESTIONS

Interested entities may submit questions to the BAA Coordinator. Answers to questions received will be posted to the same website. 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. 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: Cost Reasonableness/Realism/Affordability

Price analysis will be performed on each 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, 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 sub-awardees 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 proposed technology.

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

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.

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 abstract. At that time, the proposer will be notified and informed of one of the following decisions:

1) ARPA-H has not selected the proposer to move forward with the submitted abstract;
2) ARPA-H requests that the proposer submit a full proposal;
3) 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.

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;

2. ARPA-H has selected the proposal for funding pending award negotiations, in whole or in part. Official notifications will be sent via email to the Technical POC and/or Administrative POC identified on the proposal coversheet.
3. ARPA-H requires an explanation of any unclear elements in the submitted proposal. Based on that discussion, ARPA-H may not select the proposal, select and enter into negotiations, or require proposal revisions prior to making a selection decisions.

6.2.ADMINISTRATIVE AND POLICY REQUIREMENTS

6.2.1. Meeting and Travel Requirements

There will be a program kickoff meeting after award and all awardees are required to attend. A community Symposium will also be organized within the first three (3) months of performance as described above; the principal investigator for each team, at the minimum, will be 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 will 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 OTs, performers will be required to register in and 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

Points of Contact:

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

Collaborative efforts/teaming are encouraged. Interested parties should submit a one-page profile with their contact information, a brief description of their technical capabilities, and the desired expertise from other teams, as applicable.

8. Other Information

ARPA-H will host a Proposers' Day in support of the PSI Program on the date listed in Part I., *Overview Information* of this BAA. The purpose is to provide potential proposers with information on the PSI program, promote additional discussion, and encourage team networking.

Interested proposers are not required to attend, and materials formally presented at Proposers' Day will be posted to 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. To participate in the event, proposers must complete the online registration form located at https://arpa-h-psi.powerappsportals.us/.

Participants are required to register no later than the date listed in Part I., *Overview Information* of this BAA. This event is not open to the press or patients. ARPA-H, however, will host a patient engagement event within 3 months of launching the program, which is meant to provide patients with information on the PSI program and promote additional discussion. To facilitate easier access to underserved communities, Proposers' Day will be a hybrid event.