INNOVATIVE SOLUTIONS OPENING

FOR

AGENTIC AI-ENABLED CARDIOVASCULAR CARE TRANSFORMATION

(ADVOCATE)

Scalable Solutions Office (SSO)

ARPA-H-SOL-26-142
January 13, 2026

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Innovative Solutions Opening (ISO) Summary

Federal Agency – Advanced Research Projects Agency for Health (ARPA-H) Scalable Solutions Office

ISO Title - **A**gentic AI-**E**nable**D** Cardio**V**ascular **CA**re **T**ransf**O**rmation (ADVOCATE)

Announcement Type – Innovative Solutions Opening

ISO Solicitation Number – ARPA-H-SOL-26-142

Anticipated Awards – Multiple Other Transaction (OT) Agreements

Dates

- Posting Date: January 13, 2026
- Proposers' Day: January 23, 2026, 8:30 AM – 5:00 PM Eastern Standard Time (EST)
- Proposers' Day Registration Deadline:
    - (In-Person Attendance) – January 21, 2026, at 5:00 PM EST or when capacity is reached, whichever comes first
    - (Virtual Attendance) - January 21, 2026, at 5:00 PM EST
- Solution Summary Due Date and Time: February 27, 2026, at 5:00 PM EST
- Proposal Due Date and Time: April 1, 2026, at 5:00 PM EST

Where to Submit

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

Resource Sharing: Resource sharing is not required but is highly encouraged.

Proposers' Day

ARPA-H will host a Proposers' Day in support of the ADVOCATE program as described in Special Notice ARPA-H-SN-26-139. The purpose is to provide potential proposers with information on the ADVOCATE program, promote additional discussions, and encourage teaming and networking.

Interested proposers are not required to attend, and materials formally presented during Proposers' Day will be posted to the ARPA-H program website. ARPA-H will not reimburse potential proposers for participation at Proposers' Day (or time and effort related to submission of solution summaries or proposals).

Innovative Solutions Opening

1. ADVOCATE Program Overview

1.1 Program Vision

Cardiovascular disease (CVD) is the most common and deadly chronic disease in America. Despite the existence of effective treatments, serious life-threatening chronic CVD conditions such as heart failure are often poorly managed. The reliance on episodic, reactive, and inaccessible clinic visits to manage these complex conditions contributes to today's poor outcomes. The Agentic AI-EnableD CardioVascular CAre Transformation (ADVOCATE) program will modernize CVD care management by enabling the development and implementation of a patient-facing autonomous agentic AI system that provides 24/7 access to scalable, safe, and effective patient-centric specialist-level cardiovascular care at a fraction of today's cost. The objective of the ADVOCATE program is to overcome both technical and structural barriers for agentic healthcare, while also supporting the development of a blueprint for regulatory, reimbursement, and clinical deployment.

The **first goal** of ADVOCATE is the development, deployment, and clinical validation of a mobile-accessible CVD agent for care navigation, diagnostic and treatment assistance, and prescriptions. The agent will provide personalized, multi-disciplinary care management functions and leverage real-time, high-quality, integrated patient data from both electronic health records (EHR) and wearables.

The **second goal** is to create a disease-agnostic supervisory agent that continuously monitors and manages the CVD agent after it has been deployed clinically. This pairing allows for real-time oversight and control of clinical AI applications.

The **third goal** is to develop a blueprint for the deployment of clinical agents in different types of healthcare settings through performance of large Scalability Studies.

This systematic approach will unlock the power of agentic AI to transform CVD management, while creating a streamlined pathway for the use of agentic AI across all chronic diseases.

1.2 Program Description and Scope

CVD is the leading cause of preventable deaths and hospitalizations in the United States. Further, CVD costs $393 billion United States Dollars (USD) per year in healthcare costs and $234 billion USD per year in lost productivity. Despite the overwhelming and largely preventable burden of cardiovascular disease, access to specialist care remains alarmingly inadequate—nearly half of all U.S. counties lack even a single practicing cardiologist, leaving millions without the expertise needed to manage and prevent CVD.

The ADVOCATE program tackles the challenge of chronic disease management by advancing agentic AI solutions that can radically improve access to high-quality care. ADVOCATE supports the development and scalable implementation of interoperable agentic tools that deliver autonomous or semi-autonomous healthcare, with a clear pathway for regulatory clearance and reimbursement.

Clinical AI agents developed through ADVOCATE will leverage reasoning capabilities of advanced generative AI models (Large Language Models (LLMs), multimodal models) to capture relevant nuances of the patient's condition, prioritize tasks, escalate findings, and take actions such as adjusting treatment plans. These agents can deliver personalized, high-quality care closer to patients while optimizing clinical resources. Autonomous and semi-autonomous agentic functions will enable clinical teams to greatly extend their reach and impact. Given the worsening clinician shortage, the more autonomous an agentic solution can be, the more likely it is to generate a significant impact at scale.

ADVOCATE also enables the full utilization of patient's inputs in daily life and clinically relevant data collected though EHRs and wearables. AI agents will take multiple steps to translate complex inputs into actionable personalized patient-facing outputs. These outputs include timely diagnoses, optimal treatment recommendations, personalized health recommendations, seamless care navigation, and clinical actions such as new prescriptions.

Ensuring safety is paramount. ADVOCATE must address unmitigated risks associated with the use of agentic AI systems in healthcare. If clinical agents are not deployed safely, patients and clinicians could quickly lose trust, squandering a historic opportunity to positively transform healthcare delivery. The safe deployment of clinical agentic AI necessitates the development of dynamic locally-deployed monitoring tools.

ADVOCATE will also support autonomous monitoring of clinical agents using low-touch and highly reliable mechanisms that enable responsive local management and external regulatory oversight. This scalable solution will foster patient trust and adoption of novel technology, enabling clinicians and health systems to integrate these tools into practice. Autonomous monitoring supports regulators with sufficient information for effective oversight, while unleashing innovators to develop impactful solutions with a clear path to commercialization.

1.2.1 Technical Areas (TA)

ADVOCATE's objective is to revolutionize the management of patients with CVD by enabling the development of:

1. **TA1 "CVD Agent":** A clinically validated, regulatory-compliant, patient-facing, multimodal autonomous AI agent system to support and deliver clinical care.
2. **TA2 "Supervisory Agent":** A disease-agnostic, independent oversight agent for real-time monitoring, auditability, and regulatory compliance, leveraging secure agent-to-agent protocols.
3. **TA3 "Scaled Implementation":** Integrated development and deployment of the agentic systems in healthcare organizations with the performance of Scalability Studies.

**Note that the CVD and Supervisory agents could both represent multi-agent systems.*

TA1: CVD Agent – Reliable Agentic Care Management

Development and deployment of a patient-facing, multimodal agentic system that performs clinical functions autonomously and semi-autonomously with the clinical team, integrated in real-time with the patient's EHR(s) and wearables.

TA1 aims to develop a clinical tool that provides care management to patients with chronic CVD, such as heart failure and post-myocardial infarction ("heart attack"). This CVD agent will be 'prescribed' to patients by their clinician (primary care physician or cardiologist) and will interact directly with them to provide continuous outpatient management. It will leverage patient's inputs and data to perform advanced clinical reasoning. This clinical AI agent will function in coordination with and as an extension of the clinical team, with the ability to adapt its functions to the clinical context and the patient's preferences.

The CVD agent will be empowered by the healthcare organization that controls it to execute pre-defined activities such as responding to patient queries, providing differential diagnoses and potential treatment plans, engaging members of the clinical team as needed, and performing selected care management e.g. modify appointments. The agent will perform selected functions that meet the Food and Drug Administration's (FDA's) definition of medical device, including autonomously managing prescription orders and changing existing prescriptions for CV conditions like hypertension, hyperlipidemia, heart failure, and atrial fibrillation. The CVD agent's 'non-device' functions will include medication management, nutrition support, virtual physical therapy, care navigation, etc.

The CVD agent will leverage clinical reasoning to make diagnostic inferences and treatment recommendations based on real-time analysis of multimodal (text, voice, video and images) patient inputs, as well as clinically relevant data from the patient's EHR and wearables. This iterative clinical reasoning relies on the CVD agent's ability to automatically source, integrate, and analyze the relevant patient data very quickly (<100msecs). This patient data integration function must be interoperable between EHR vendors and must tokenize multimodal data from wearables collecting information relevant to CVD management, such as heart rate, continuous glucose monitoring (CGMs), electrocardiogram (EKG), blood pressure, activity, and weight.

The CVD agent will perform high risk functions that need to be continuously monitored and controlled. Therefore, TA1 performers need to adapt streamlined protocols to continuously serve data that can be used for a Supervisory agent, which will be developed through TA2. It follows that TA1 performers will need to collaborate with the other performers and the ADVOCATE team on the development and implementation of a standardized protocol that enables remote visibility, monitoring, and control of the CVD agent.

Regulatory Considerations: The CVD agent must be designed as an AI-enabled medical device that would seek market authorization from FDA. The ADVOCATE team will facilitate early and frequent communication between FDA and TA1 performers. TA3 performers will be health systems that provide TA1 performers with access to EHR data, EHR production environments, and clinicians and patients assisting in user interface (UI) and user experience (UX) testing. Feedback from TA3 performers will inform CVD agent development and the Scalability Studies. TA1 performers that proceed to Phase 2 will be deployed in large Scalability Studies performed across TA3 health systems, comparing the impact of the CVD agent vs usual care in patients with heart failure or those who have had a heart attack.

Table 1 – TA1 Required Functionalities

TA1 – CVD Agent
TA1 proposals should describe their unique technical approach and product strategy towards the development of a CVD agent and share relevant prior experience as applicable for the following. Proposals should refrain from recapitulating the functionalities below; rather proposals should focus on how they intend to incorporate these functions into their tech build and how that will lead to the overall program goals of improving cardiovascular outcomes nationwide.
Agentic Execution • Provide a comprehensive strategy to develop an agentic AI framework capable of coordinated execution of pre-defined activities such as patient data analysis, clinical reasoning, response to patient queries, care management functions such as prescription changes, nutritional guidance, virtual exercise therapy, care navigation, and engagement of members of the clinical team.
Data Processing & Integration • Present a low-latency approach to real-time aggregation and integration of real-time and historical health data from sources such as EHRs and wearables. • Define automatic solution for the identification of relevant data types, selection of pertinent fields, extraction of relevant features, indexing, de-duplication, normalization, analysis, and summarization of content with efficient error handling, and context management to enable instantaneous (<100msec) responses to queries.

TA1 – CVD Agent
• Efficiency in tokenization of multimodal wearable data from multiple vendors, including preferred data streams relevant to CVD such as EKGs, blood glucose, heart rate, blood pressure, activity, and weight. • Share system for agentic system to connect patients through native apps, secure web applications, or HIPAA-compliant calls and texts to deliver context-aware, personalized messages while adhering to FDA and industry standards for privacy and cybersecurity. These standards may be updated during phase transitions to reflect industry advances.
Care Management • Develop a strategy to generate differential diagnoses and autonomous treatment recommendations based on patient data and clinician input. The strategy could enable patient offerings such as tailored health coaching and goal setting, management of care logistics such as appointments and prescriptions, automatic documentation of interactions and outcomes, and predictive analytics to anticipate clinical outcomes for chronic CVD, adjusting interventions accordingly. • Produce protocols for accurate, timely, and efficient clinical triage and task assignment to human members of clinical team in situations requiring urgent response.
External Monitoring & Control • Design protocol for secure, low-latency communication with the Supervisory agent, and TA3 performers. This protocol should enable continuous tracking of outputs, allow live evaluation and control of the CVD agent by the Supervisory agent.
Interoperability • Develop protocol to ensure interoperability through APIs, including Fast Healthcare Interoperability Resources (FHIR) for standardized data exchange, HL7v2 for legacy system compatibility, national HIE network APIs for accessing patient data, custom APIs for integrating wearable data, and clinical operations APIs for connecting with existing healthcare tools and workflows.
Identity & Access Management • Implement end-to-end encryption, role-based access controls (RBAC), comprehensive audit logs, and privacy-preserving AI techniques, ensuring compliance with HIPAA, GDPR, and NIST Cybersecurity Framework.
Development & Lifecycle Management • Provide a development plan and technical specifications for building autonomous AI agents on pre-trained LLMs or multimodal foundation models , supporting model drift monitoring, continuous learning, and human-in-the-loop feedback (RLHF). Please include mechanisms to prevent harmful actions and ensure ethical, patient-centered decision-making. • Produce a system which allows for the real-time monitoring of cybersecurity, data reproducibility, user permissions, and auditing requirements. • Propose a method for continuous learning, regular model and UX updates, regulatory authorization, and tools for testing and validation.
Out of Scope • Foundation model being developed from scratch. • Technologies not being developed for FDA authorization. • Solutions lacking interoperability with Supervisory agents and industry's standard orchestration frameworks.

TA2: Supervisory Agent – Automated Clinical Agent Monitoring & Control

Development of a disease-agnostic Supervisory agent that can continuously monitor and control clinical agents

TA2 will focus on the development of a scalable and context-aware Supervisory agent that enables effective regulatory oversight of clinical agents while placing minimal burden on health systems. This Supervisory agent will perform automated continuous monitoring and control of clinical agents, thus playing a pivotal role in local management and regulatory post-marketing monitoring of the deployed clinical agents' safety and performance.

The Supervisory agent will operate alongside the CVD agent within the ADVOCATE program, continuously evaluating both patient inputs and the CVD agent's outputs. Its primary focus will be on assessing risk (from action or inaction), acuity, accuracy, and the level of uncertainty in the CVD agent's reasoning. The Supervisory agent will determine whether outputs or actions can safely proceed or whether they should be routed to a clinician for review. Both agents will incorporate a human feedback loop, enabling the clinical team to provide reinforcement learning from human feedback (RLHF) and drive continuous performance improvement. Additionally, the Supervisory agent will monitor for dips in clinical reasoning and trigger a hard-stop analysis with a transition to safe mode when necessary.

The overarching goal of TA2 is to get past the current paradigm where providers need to review and approve model outputs before clinical intervention. The development of a Supervisory agent allows for the safe and efficient scaling of AI in healthcare. The Supervisory agent will streamline the development, regulatory review, and post-deployment oversight of clinical agents by dynamically assessing diverse clinical outputs and capturing insights from interactions with the clinical team. The Supervisory agent development will rely on inputs from TA3 health systems and have a mission-critical role in safety assurance of clinical agents, by independently detecting and preventing potential errors in real-time.

Regulatory Considerations: The Supervisory agent will need to fulfill the requirements for qualification as a Medical Device Development Tool (MDDT) by the FDA, which would allow it to become the industry standard tool for generative and agentic AI monitoring; therefore, enabling this industry to scale considerably. While this Supervisory agent will be tuned and validated within the context of ADVOCATE, the goal is to be disease and agent agnostic, capable of evaluating and supporting future clinical agents with different intended uses.

The ADVOCATE team will facilitate early and frequent communication between FDA and TA2 performers. Via health systems that are selected as TA3 performers, TA2 performers will have access to EHR data, EHR production environments, and clinicians that will assist in UI/UX testing. The TA2 performers selected to proceed to Phase 2 will be deployed in

large Scalability Studies performed across TA3 health systems, comparing the impact of the CVD agent vs usual care, simulating a post-market monitoring environment.

Table 2 – TA2 Required Functionalities

TA2 – Supervisory Agent
TA2 proposals should describe their unique technical approach and product strategy and share relevant prior experience towards the development of a supervisory product. Proposals should refrain from recapitulating the functionalities below, rather they should focus on how they intend to incorporate them into their product. Proposals should also include the framework for agentic monitoring that they will employ. They should also share why they believe their approach will be successful. TA2 Supervisory agents will need to be integrated with the TA1 CVD agent but are also required to function independently as monitoring agents capable of being integrated with other, non-CVD-related agentic AI solutions. TA2 solutions are strongly preferred to be open source.
Clinical Agent Monitoring • Deliver a product proposal that evaluates clinical recommendations across diseases, assessing quality, risk, and reliability while monitoring patient acuity, errors, and algorithmic drift.
Clinical Agent Management • Show how your product will trigger clinician intervention when needed, maintain comprehensive audit logs of all clinical agent activities, and continuously monitor clinical guidelines and compliance and regulatory standards. These standards may be updated during phase transitions to reflect industry advances.
Regulatory Support • Provide a system which allows useful data transfers to regulatory bodies for oversight, de-identifies and aggregates data, and has protocols for rapid issue triage and resolution.
Data Integration • Facilitate real-time product integration with the CVD agent to ensure appropriate monitoring and oversight of the overall customer experience.
Interoperability • Present an interoperability framework leveraging Application Programming Interfaces (APIs) and Model Context Protocol (MCP) while adhering to FDA and industry standards for privacy and security.
Development & Life Cycle Management • Design a system that adapts to new clinical knowledge, guidelines, and regulatory requirements, supports continuous learning, model drift monitoring, human-in-the-loop feedback (RLHF), allows for rigorous testing and validation to ensure accuracy and effectiveness, and complies with FDA and industry standards for interoperability, privacy, and security. These standards may be updated during phase transitions to reflect industry advances.
Out of Scope • Foundation model being developed from scratch. • Solutions that are not disease agnostic. • Technologies not being developed for FDA MDDT qualification. • Solutions lacking interoperability with Supervisory agents and industry-standard orchestration frameworks.

TA3: Scalable Implementation – Integration of Clinical Agents in Healthcare Organizations

Integration of the CVD and Supervisory agents with EHR Data and Clinical Workflows within Health Care Settings and Evaluation in Large Scalability Studies

The healthcare organizations selected as TA3 performers will **1)** Engage proactively with TA1 and TA2 performers to establish a feedback loop bringing clinical insights into agentic AI development, **2)** Provide access to their EHR data and pre-production environments to fine-tune and integrate the agents, **3**) Develop governance frameworks to integrate agentic functions within the clinical workflow, **4)** Collaborate with the Independent Verification & Validation (IV&V) partner on the design and implementation of TA1 and TA2 evaluation processes, and **5)** Perform the large Scalability Studies comparing outcomes of patients between the CVD agent and usual care, while also validating the use of the Supervisory agent for post-market surveillance of clinical agents.

In Phase 1, each TA3 performer will engage with TA1 and TA2 performers from program initiation, providing seamless access to data for tuning, access to appropriate clinical team members for UI/UX, and will work with their EHR vendors to ensure appropriate integration into the system. This iterative process will therefore enable TA3 performers to implement clinical agents that are planned, built, and properly integrated into their environment.

Early engagement of TA3 performers will enable the CVD and Supervisory agents to be assembled with input from end-users and implemented in the Scalability Studies in accordance with their unique organizational preferences, clinical operations tools (e.g., scheduling, pharmacy benefits, care navigation, etc.), and care management capabilities. TA3 performers therefore will define the *modus operandi* of their clinical agents, which will become a digital member of their clinical care team. Agentic systems deployed in different healthcare settings through TA3 will play a critical role in developing a blueprint for other healthcare organizations implementing clinical and supervisory agents into clinical care.

In Phase 2, TA3 performers will perform Scalability Studies that best mirror anticipated clinical deployment in their setting, randomizing patients to those receiving the agentic intervention vs those receiving usual care. The Scalability Studies will also be designed to generate evidence regarding the agentic system's cost-efficiency and safety, that would inform reimbursement decisions from payers such as the Centers for Medicare and Medicaid Services (CMS).

TA3 performers will function as a testbed for the CVD and Supervisory agents. They will collaborate with the IV&V Partner and the ADVOCATE team on the development and optimization of the evaluation metrics to track progress made by TA1 and TA2 performers. They will also be required to map clinical processes, adapt systems, and integrate tools to deploy and evaluate the clinical agents in close collaboration with TA1 and TA2 performers. The AI implementation achieved through TA3 will allow the conduct of Scalability Studies,

which will ultimately address the challenges of evaluating clinical agents across varied healthcare organizations. While these Scalability Studies will be conducted independently by TA3 performers, they will apply standardized methods across all organizations to determine the safety and effectiveness of clinical and supervisory agents in representative real-world environments.

To foster national scalability, ARPA-H intends to select TA3 performers with variance in business model, payer type, EHR vendor, and organizational structure (e.g., health systems, medical groups, Accountable Care Organizations (ACOs), etc.). ADVOCATE also aims to include testing and coverage in geographies with access to the target population where there is also a greater-than-average need for access to clinical agents. A multi-site implementation will allow a real-world evaluation of TA1 and TA2 performers being deployed in multiple clinical environments in areas of critical need across the country.

Table 3 – TA3 Required Activities

TA3 – Scalable Implementation
Development • Describe the capacities of the healthcare system to supply high-quality longitudinal EHR data to fine-tune CVD and Supervisory AI agents, set clear boundaries for autonomous decision making by requiring clinician approval for high-risk scenarios, and perform integration testing in pre-production environments to validate clinical functions and order entry capabilities.
Integration • Outline how the healthcare system's IT team will integrate EHR, Hospital Information System, and Enterprise Resource Planning platforms with the CVD and Supervisor agents for real-time data processing and documentation, connect billing systems for streamlined claims, enable patient interactions through existing portals, and structure how the clinical team and agentic system will interact in specific scenarios.
Clinical Validation • *EVALUATION*: Explain how the healthcare system plans to collect key clinical performance metrics, conduct error and accuracy assessments, and measure clinical and operational outcomes to evaluate CVD agent effectiveness via the Supervisory Agent. Additionally, describe how it would monitor the clinical team engagement and solution uptake. • *IMPROVEMENT*: Relate how the healthcare system proposes to incorporate continuous feedback and learning to refine AI agents, adjust training and engagement strategies based on real-world use, and enable efficient adaptation to new data and guidelines.
Out of Scope • Proposals inhibiting TA1 and TA2 access to EHR data or production environments. • Proposals that don't detail clinician engagement for UI/UX.

1.2.2 Program Structure & Timeline

The ADVOCATE program is a two-phase, 39-month program divided into the following phases:

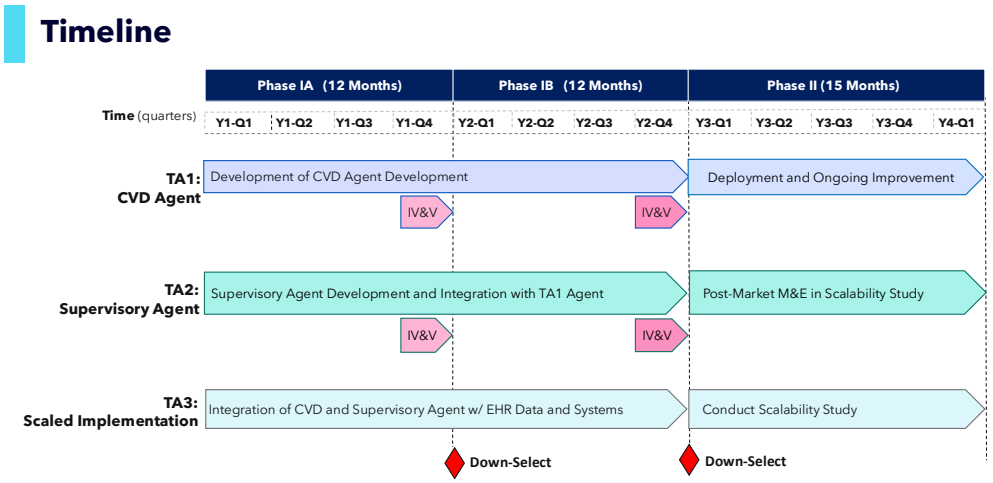
- Phase 1A (Base Period): 12 months
- Phase 1B (Option 1): 12 months
- Phase 2 (Option 2): 15 months

Multiple awards are anticipated, and it is expected that not all performers will be selected to move forward into each phase. After awards have been made to TA1, TA2, and TA3 performers, the ARPA-H ADVOCATE program management team will host a kickoff meeting to foster collaboration, encourage cooperation, and facilitate data and information sharing. TA1 and TA2 performers are encouraged to propose the use of industry standards for interoperability and orchestration. These standards may be updated during phase transitions to reflect industry advances.

Throughout the program, the ARPA-H ADVOCATE program management team will hold monthly virtual meetings with performers to review technical progress and address barriers to success. These meetings provide a forum for teams to report progress, identify challenges early, and provide an opportunity for the management team to understand and address barriers to technical success.

Continued performance of awardees through all phases of the program will be at the sole discretion of the Government, and may be based on several factors, including technical progress measured again the metrics and milestones defined in this ISO, and availability of funding.

Image 1 – Program Timeline



Phase 1A (12 months) – Solution Development

The goal of Phase 1A is for TA1 and TA2 performers to develop a prototype technology meeting the requirements outlined, culminating in an IV&V study that will inform down-selections. AI agents will be individually developed and trained on top of a foundation model with a combination of at least semantic knowledge, patient-doctor conversations, and EHR and wearable data with a goal of developing an integrated multi-agent system. To achieve this, TA1 and TA2 performer teams will be required to pool data access and resources to integrate their technologies into one, multi-agent product. The program goals listed below are required to be included in the Statement of Work.

- **6-month Goal:** TA1 and TA2 performers will each have initial prototypes that can enter alpha testing for a subset of use cases with patients and clinicians for the relevant TAs. These prototypes will be developed using EHR data provided by TA3 performers.
- **9-month Goal:** Expanded prototypes covering improvements to existing use cases and additional ones will be developed for formal evaluation in the Phase 1A IV&V study using simulated, synthetic patients. This will inform formal Phase 1A down-selections. UI/UX testing of prototypes with clinicians and patients will be done in the TA3 performer health care systems.
- **12-month Goal**: TA1 performers will have developed Agentic prototypes that can demonstrate non-inferiority vs cardiologists for treatment, empathy, and reasoning with low latency. TA2 performers will have developed low-latency Agentic prototypes capable of ascertaining the accuracy and determination of clinical acuity and intervention risk for the TA1 agent. TA3 performers will have facilitated TA1 and TA2 agent integration and access to patient data from EHR and wearable/ Remote Patient Monitoring (RPM) platforms, provided clear guidance for CVD agent implementation within EHR interfaces and clinical workflows, developed comprehensive mapping of clinical resources and workflows, and developed a thorough impact assessment with defined risk mitigation strategies and accountable teams. TA3 performers will have begun incorporating TA1 and TA2 agents in their pre-production EHR systems. At the 12-month mark, based on program management team's evaluation and results of the IV&V study, some TA1 and 2 performers may be down-selected with the others advancing to Phase 1B.

Phase 1B (12 months) – Integration and Validation

The goal of Phase 1B is for TA1 and TA2 performers to develop a technology that is ready to be submitted to FDA for authorization or qualification, and meets all the requirements outlined, culminating in an IV&V study that will inform down-selection.

- **18-month Goal**: Each performer team will have a solution prototype ready and will have held formal meetings with FDA for their technologies. TA3 performers will begin prototyping the clinician interface, beginning the process of seeking Institutional Review Board (IRB) approval for the Scalability Studies, and performing FDA Investigational Device Exemption (IDE) studies.
- **21-month Goal:** Release candidates developed by TA1 and TA2 performers will undergo an IV&V evaluation in which human users/patients with EHR profiles will be used to compare TA1 performance vs cardiologists using actual or simulated patients with EHR profiles based on metrics described subsequently. TA1 and TA2 performers will be selected to advance to Phase 2 based on IV&V results, target product evaluations, and overall product quality as assessed by the PM team.
- **24-month Goal**: TA1 and TA2 performers will have finalized release candidates ready for deployment that can implement remote updates and improvements based on patient and clinician feedback from the Phase 2 Scalability Study. TA3 performers will have established a clinical study team and infrastructure, secured IRB approval and patient recruitment plans, implemented clinician and patient engagement resources, integrate and automate CVD agent within EHR interfaces and clinical workflows, and guided by organizational objectives and Supervisory Agent inputs.

Phase 2 (15 months) – Scalability Studies

TA3 performers will integrate, deploy, and evaluate the top performing CVD and Supervisory agents in their clinical workflows in Phase 2. Each TA3 performer is expected to adapt the agents so that it fits their workflows, needs, and infrastructure.

TA3 performers will also design and execute independent Scalability Studies and will have three main objectives:

1) Assess the clinical performance and outcomes of the CVD agent in a real-world scenario versus usual care,

2) Collect cost and utilization data that would inform models for reimbursing agentic AI-enabled clinical care, and

3) Access the effectiveness of the Supervisory agent as a decentralized post-market monitoring solution to dynamically oversee and audit the performance of clinical AI agents deployed in patient care.

CVD agent will be monitored to determine the appropriateness of agentic functions (e.g., care navigation, prescriptions, etc.), how the patients use them, how the solution saves time for the clinical team, and how it improves treatment adherence. Clinical outcomes

monitored will include HF/CVD Hospitalizations, ED/UC visits, CV death, and serious adverse events.

The Supervisory agent will be continuously monitored on its effectiveness in tracking the CVD agent activities in a way that provides sufficient safety assurance to the healthcare organizations deploying the solution and external entities interested in remote agentic AI oversight, such as the FDA.

The target population will be individuals who are post-myocardial infarction or have heart failure. Patients can be enrolled through outpatient clinics or from the inpatient setting prior to discharge. Adequate representation of older adults will be important both in development but also in validation studies. The intended population must align with the intended use of the AI agent.

1.2.3 TA-Specific Development Timelines & Metrics

TA1 – CVD Agent

In **Phase 1**, the CVD AI agent will be trained to develop robust clinical reasoning capabilities to make decisions regarding chronic CVD management using EHR, wearable, and sematic data.

In the **Phase1A** development period, performers can use their own data in addition to the EHR data and environments provided by TA3 performers to train and tune their agents. Phase 1A training will include semantic CVD knowledge including clinical guidelines and protocols, patient-doctor conversations, clinical research and education resources. UI/UX testing and optimization leveraging feedback of prospective patients and clinicians will also be critical in this phase of development.

Aggressive integrated TA1 & TA2 product development will be followed by an IV&V study that will start at the 9-month mark. At the 12-month point, performers will undergo a down-selection process. This down-selection will be made by the ARPA-H team and will be partially informed by results from the IV&V study (using synthetic data), evaluation of the performer's technical performance up to that point, and the availability of funding

Selected performers will begin **Phase 1B**, which will focus on developing an FDA-regulated patient-facing product that is fit for deployment and capable of achieving non-inferiority in key domains such as diagnostic accuracy, treatment plan quality, contextual awareness, empathy/communication abilities, clinical reasoning, and appropriateness of agentic actions when compared to human clinicians. Performers will have 9 months to complete integrated product development as the second IV&V study begins at month 21, followed by a second down-selection at 24 months. The 9 months before the IV&V study will allow performers to: 1) perform extensive UI/UX testing with human subjects, 2) integrate the product with all TA 3 performer systems and with wearables, and 3) collect data required

for regulatory submission based on feedback performers receive from 513g meetings with FDA.

Phase 1B will conclude at 24 months with a uniform study conducted across performers comparing performance of the AI agent vs cardiovascular specialists for a variety of simulated patient scenarios. Continuation into Phase 2 will be determined by ARPA-H and will be based on technical progress made in prior phases and available funding. **Phase 2** will entail the conduct of Scalability Studies involving large health systems in 'real world' settings evaluating the agent's capabilities.

Table 4 – TA 1 Metrics by Phase

	TA1 Metrics	Phase 1A	Phase 1B
Effectiveness	Non-inferiority vs cardiologists for diagnosis, treatment, empathy, and reasoning	W/ Synthetic Data	W/ Simulated Patients
	Appropriateness of Agentic Actions (care navigation, prescriptions, patient data processing, etc.)	>85%	>95%
	Appropriateness of Triage	>85%	>95%
	Serious error rate	<5%	<3%
Patient Experience	Proportion of interactions where clinical agent effectively adapts to patient preferences	>90%	>95%
	User Acceptance Test (UAT) score	>85	>95
Data Integration	Effective selection of relevant records (pass rate in manual review of sample)	>93%	>95%
	Ability to process FHIR and HL7v2 records (ratio of successful/failed transactions)	>95%	>97%
	Data summarization proficiency (reduction of token count of processed records)	>40%	>50%
	Summarization quality score (retention performance with Claim Recall method)	>80%	>85%
	Proportion of errors auto-corrected (count of fixes/total error events)	>85%	>90%
Usability	Number of supported EHR vendors	1+	2+
	Number of integrated wearable or RPM devices	1+	2+
Efficiency	Time to complete record processing (seconds/typical medical record)	<2s	<0.1s

	TA1 Metrics	Phase 1A	Phase 1B
	Response latency (round-trip time of query-response in audit logs)	<3s	<1s
	Computational cost (cost/processed record)	<$0.50	<$0.05

TA2 – Supervisory Agent

In **Phase 1**, performers will have access to the common EHR data acquisition and the EHR data and environments of TA3 performers. Independent model development and training from TA1 is essential to prevent overfitting and minimize 'AI sycophancy'. In **Phase 1A** the Supervisory agent will be trained on general medical knowledge and EHR data from TA3 performers but validated and tuned for CVD throughout the program. Performers will develop and implement their framework to enable semi-autonomous surveillance of clinical generative and agentic AI. Emphasis will be placed on the agent's ability to assess the clinical context of patient prompts and the risk and uncertainty associated with CVD agent outputs. The Supervisory agent's primary function will be to monitor for safety and accuracy. An IV&V study starting at the 9-month mark using synthetic data will inform a down-selection phase in which selected performers will advance into Phase 1B.

Down-selection at the 12-month mark will be based on results from the IV&V study, evaluations of the technical performance performed by ARPA-H, and available funding. After initial model development, **Phase 1B** will focus on incorporating inputs from human clinical adjudicators and continued improvement including through reinforcement learning from human feedback. Validation with manual review will be needed to improve performance. Performers will also have continued facilitated meetings with FDA such that they are on path for submitting their tools for qualification as FDA MDDT. Supervisory agents will also be integrated in tandem with the CVD agent into the EHR systems of TA3 performers. In **Phase 2**, the Supervisory agent that continues past the 24-month down-select will be deployed in health systems as a post market monitoring tool in Scalability Studies. Its performance in error adjudication and safe performance of autonomous tasks will be critical.

Table 5 – TA2 Metrics by Phase

	TA2 Metrics	Phase 1A	Phase 1B
Effectiveness	Ability to ascertain accuracy of clinical agent	>85%	>95%
	Recognition of high-quality treatment recommendations	>85%	>95%
	Quantification of hallucination rate	>85%	>95%
	Determination of uncertainty of clinical inference	>85%	>95%
	Determination of clinical acuity and intervention risk	>90%	>97%
	Evaluation of appropriateness of task assignment to clinical care team members	>90%	>97%
	Ability to ascertain accuracy of clinical agent	>85%	>95%
Usability	Clinician app User Acceptance Test (UAT) score (0 –100)	>80	>90
	Response latency (round-trip time of query-response in audit logs)	<3s	<1s
	Quality score (0-100) of summarized information provided to the clinical team	>80	>95

TA3 – Scalable Implementation

In Phase 1, TA3 performers will provide access to EHR data and pre-production environments to develop, train, and tune TA1 and TA2. Performers will also begin the process of integration and deployment of TA1 and TA2 into their systems and design the Scalability Studies that will be used for evaluation. TA3 performers will provide key technical integration metrics and criteria to TA1 and TA2 by end of month three. TA3 performers may be down-selected if they fail to meet the metrics summarized in the table below. TA2 performers will be expected to prove all TA1 and TA2 performers access to and integration with TA3 EHR systems by the 3-month mark, and ability to start Scalability Studies 3 months after initiation of Phase 2. Study design will be developed in partnership with TA1 and TA2 performers and the ARPA-H ADVOCATE team.

Table 6 – TA3 Metrics by Phase

	TA3 Metrics
	Phase 1A
Access & Guidance (within first month)	Effective access to patient data from institutional EHR and connected wearable/ RPM platforms
	Effective guidance for the integration of CVD agent with main EHR interfaces (e.g., patient portal, visit scheduling, post-discharge) and the clinical workflow
Implementation Plan	Detailed mapping of clinical resources and workflows informing implementation plan for agentic solution
	Complete impact assessment with delineation of risk mitigation approaches and establishment of accountable teams
	Phase 1B
Preparation for Scalability Studies	Establishment of clinical study team & infrastructure (e.g., EHR dashboard) to manage CVD agent use and outcomes
	Preparation for study conduct, including IRB approval, patient recruitment plan, and implementation of clinician and patient engagement resources
EHR & Clinical Integration	Integration of CVD agent with main EHR interfaces (e.g., patient portal, visit scheduling, post-discharge) and the clinical workflow
	Automated CVD agent control implementation based on organizational objectives and inputs from Supervisory agent

1.2.4 IV&V Partner

The ADVOCATE program will rely on a government-chosen IV&V Partner to conduct impartial studies that inform performer team down-selection at the transition between Phase 1A- Phase1B and Phase 1B- Phase 2. These studies will start at the 9-month and 21-month mark and be completed in 2 months. A delay in start and/or completion of any of the IV&V studies of any of the performer teams will need to be avoided as it can delay the entire program. Therefore, these studies will be precisely planned, prepared, and executed to prevent program delays. The Phase 1A IV&V study will compare agentic performance using synthetic data and simulated patients. The Phase 1B IV&V study will include real users/patients interfacing with the agents vs actual cardiologists.

ARPA-H is not soliciting IV&V proposals as part of this solicitation.

The government-chosen IV&V Partner will closely engage with TA1, TA2, and TA3 performers beginning from the ADVOCATE program kickoff meeting. Virtual site-visits will be conducted by the IV&V Partner to confirm TA1 and TA2 agents are being developed in alignment with program metrics and milestones. The IV&V Partner will also collaborate closely with TA3 performers and members of the ADVOCATE program team on the development and optimization of the evaluation metrics to track progress made by TA1 and

TA2 performers. It will also be responsible for evaluating the limits of the agents with the testing using edge-case scenarios. Data collected throughout the IV&V process across phases will meet FDA criteria and can be part of authorization and qualification applications submitted to FDA by TA1 and TA2 performers.

1.2.5 Performer Collaboration Expectations

Table 7 – Performer Collaboration Expectations

TA	Collaboration Expectations
All	• All performers will develop and agree to an Associate Performer Agreement, which will specify how data and information will be shared within and across performer teams. • Performers agree to open data sharing between TA teams and IV&V Partners as needed to facilitate integration of AI agents, deployment in Scalability Studies, and validation and verification of the agent's technical capacity. • All TA performers agree to collaborate with FDA as needed to achieve authorization for the developed agent.
TA1	• TA1 performers will collaborate with TA2 performers to ensure the CVD agent is developed in a way that allows for seamless integration with the Supervisory agent. Specifically, connecting with a common API used by TA2 performer teams. • TA1 performers will collaborate with the IV&V partner to efficiently and effectively evaluate the TA1 CVD agent and verify it aligns with the TA1 metrics and milestones. • TA1 performers will collaborate with TA3 performers to receive clinical insights during agent development, engage with TA3 performers to execute UI/UX testing, and to coordinate on the product deployment throughout the period of performance.
TA2	• TA2 performers will collaborate with TA1 performers to ensure the Supervisory agent is developed in a way that allows for seamless integration with the CVD agent. Specifically, connecting with a common API used by TA1 performer teams. • TA2 performers will collaborate with the IV&V Partner to efficiently and effectively evaluate the TA2 Supervisory agent and verify it aligns with the TA2 metrics and milestones. • TA2 performers will collaborate with TA3 performers to receive clinical insights during agent development, engage with TA3 performers to execute UI/UX testing, and to coordinate on the product deployment throughout the period of performance.
TA3	• TA3 performers will collaborate with TA1 and TA2 performers to offer clinical insights during Agent development, allow access to EHR data and pre-production environments, provide clinicians to support in UI/UX testing of agents, and to coordinate on the product deployment throughout the period of performance. • TA3 Performers will collaborate with the IV&V partners and the ADVOCATE team on the development and optimization of the TA1 and TA1 evaluation metrics.

Commercialization Strategy for TA1 and TA2 Performers

It is expected that TA1 and TA2 performers will submit a commercialization strategy narrative during the period of program performance, which demonstrates that the proposer team has considered the commercial path of their work and brings the necessary expertise and partnerships to do so. This early program milestone needs to include the following sections:

- Executive Summary
    - In this section, address market need and potential options for transitioning the technology (e.g., Licensing, spin-out, etc.). Address whether there are alternative off-ramps for any sub-technologies that may be developed alongside the primary technology (diagnostic, digital twin platform, therapeutic, etc.). Please be specific about what you think success looks like.
- Commercialization Strategy
    - Provide a narrative to address overall approach to end user/market, business model, IP, regulatory and transition/exit plan including any recommended proposed changes to the commercial roadmap (see Appendix E).
- Available Commercialization Resources and Expertise
    - In this section, describe the commercialization resources you have available to address commercialization milestones (e.g., product development and prototyping facilities, IP management resources, regulatory affairs support, financial resources and fundraising experience, etc.).

The commercialization strategy narrative must be no longer than two pages. Appendix E of this ISO includes additional information and an example commercialization roadmap that may be helpful in scoping this section.

Management Plan

It is expected that TA1, TA2, and TA3 performers will submit a management plan during the period of program performance as an early program milestone. Specifically, the management plan will need to include the following sections:

- Provide a summary of the expertise of the team, including any sub-performers, and key personnel who will be doing the work. A Principal Investigator (PI) for the project must be identified, along with a description of the team's organization, including the breakdown by TA. All teams are required to identify a Project Manager.

- 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-performers of the proposed effort. Include risk management approaches. Describe any formal teaming agreements required to execute this program.

Expectations of Collaboration and Data Sharing Between TA1 and TA2 Performers

The successful fusion of TA1 and TA2 agents into a single multi-agent system will depend on the effective integration by TA1 and TA2 teams during development. To enable this, all selected TA1 and TA2 performers will agree to a data management plan (see section 2.3.3), guaranteeing the data open access and collaboration needed to meet the ADVOCATE program's technical goals.

As outlined in the data management plan section, TA1 and TA2 performers will be expected to share deidentified/sanitized project data with other ADVOCATE performers and, potentially, federal agencies to promote transparency and collaboration. Detailed plans for data storage, computing, and management challenges are required and may be updated with ARPA-H approval as the program evolves. The Data Management and Sharing Plan (DMSP) should use industry-standard formats for compatibility with ARPA-H and federal platforms. Solution summaries and full proposals must address data management and sharing protocols.

For teams that are submitting proposals for TA1 **and** TA2, attention needs to be paid to ensure TA1 and TA2 remain technically independent, to allow for accurate evaluation of the CVD agent by the Supervisory agent.

The TA1 and TA2 performers will also need to collaborate on the development of a standardized Remote Monitoring & Control open-source protocol for secure low-latency (<100msecs) communication between the CVD and Supervisory agents. This protocol will enable continuous tracking and analysis of clinical reasoning utilized in multi-turn patient-agent interactions and in the context-aware interpretation of patient data by a Supervisory

agent. It will also allow an (external) Supervisory agent to securely exert direct live control and changes in operational settings for care management functions. This protocol will also enable the automated tracking of clinical outcomes and key operational metrics by the (external) Supervisory agent.

2. Eligibility Information

2.1 Eligible Proposers

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

2.1.1 Prohibition on Performer Participation from Federally Funded Research and Development Centers (FFRDCs) and Government Entities

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

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

2.1.2 Current Professional Support

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

2.1.3 Non-US Entities

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

2.2 System for Award Management (SAM)

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

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

2.3 Proposer Team Structure

Due to the need for inter-team cooperation in the ADVOCATE program, it may necessitate varying levels of participation from entities with unique expertise across phases and tasks of the program. For instance, all TA3 performer health systems will need to integrate agentic AI solutions developed by TA1 and TA2 performers, which will require substantial coordination. TA1 and TA2 will also be required to embrace interoperability, modularity, and scalability across multiple clinical settings in their product development approaches.

To meet this need for collaboration, offerors may choose to submit a proposal as a prime/sub-performer team or as a multi-party team. Offerors should identify the teaming arrangement most suitable to their specific combination of expertise, capabilities, and execution plan. In addition to inter-team collaboration, it is expected the project manager

of each team will communicate consistently with the ARPA-H ADVOCATE team to overcome technical hurdles and discuss progress.

Regardless of the selected teaming approach, offerors are required to submit one, singular proposal, per TA proposed, that responds to all of the requirements stipulated by this ISO.

2.3.1 Prime/Sub Teaming Approach

The prime performer/sub-performer teaming arrangement is the more "traditional" teaming structure approach. It is anticipated to be utilized by teams who wish to have a single prime performer be responsible for interactions with the government and sole responsibility for the performance of the project. The prime performer is responsible for all negotiations, managing the sub-performers, and addressing any administrative or performance issues. The prime has the sole responsibility for team management and program execution. In this teaming arrangement, leadership may not be changed for the full duration of the project and sub-performers do not have direct interaction with government partners. Privity of contract is solely between the government and the prime.

2.3.2 Multi-Party Teaming Approach

The multi-party teaming arrangement is anticipated to be utilized in a team wherein a group of organizations and/or performers work together to accomplish a common goal, with members sharing resources, knowledge, and expertise. While one team member is usually elected to serve as the lead member or authorized (human) agent for administrative purposes, such as executing documents or receiving payment on behalf of the team, each member must be bound to the team membership agreement and must be a party to the resultant OT award with ARPA-H. In this type of team structure, each member must perform substantive technical work as part of the team. This approach is also not exclusive to a single technology developer and a single product sponsor. Instead, it can involve larger groups of developers and sponsors who may have ready applications for the developed tools within their current development pipelines.

Unlike a prime/sub arrangement where the prime performer is the leader of the team throughout the duration of the project, the multi-party teaming structure allows different members of the team to take the lead role at different stages of the program life cycle based on expertise and experience, as needed. Additionally, the team structure allows for changes in team membership whenever necessary and enables new partners to join the team. The multi-party team arrangement allows for dynamic changes as needed throughout the course of performance, allows for open communication between the government and all performers on a team, and ensures that all team members are responsible for performance and invested in the success of the program.

This approach supports collaboration among multiple developers and sponsors, enabling teams to pursue technology development, proof-of-concept, and adoption throughout the

ADVOCATE program. Unlike a prime/sub arrangement, leadership can shift among team members based on expertise, and team membership can change as needed, allowing new partners to join. All members are responsible for performance and program success, and open communication with the government is encouraged.

Teams are formalized through a teaming agreement ("articles of collaboration") that outlines roles and responsibilities. The government is not a party to this agreement and does not dictate its terms. Team members decide how to manage membership and internal arrangements, including allowing members to join or leave as needed.

A multi-party team structure offers several advantages over a traditional prime/sub-performer model. It fosters collaboration, often leading to lasting partnerships, and gives the government direct contractual relationships with all team members. This structure provides the government with greater visibility, enables direct communication, ensures shared responsibility for performance, and allows for flexible leadership and membership changes as the project evolves.

If proposers decide to use a multi-party teaming approach, they are required to follow these minimum requirements:

1. Subcontracting is allowed only for non-essential work; all substantive contributors must be team members.

2. A team member must be designated to handle administrative functions and act as (human) agent or lead and must also contribute substantive technical work.

3. A fully executed teaming agreement outlining roles and responsibilities must be in place before award. All team members must be parties to the OT agreement. The lead performing organization must be able to change during the project if needed. The agreement must cover the full scope of the ADVOCATE program. The government will not approve the agreement but will require proof that it has been executed by all team members before making an award.

Proposers pursuing a multi-party teaming approach will still be required to submit stand-alone solution summaries and full proposals for **each** TA they are interested in. Please note: If a proposer team submits a proposal for TA1and TA2 it is possible that only one of the proposals, either TA1 or TA2, may be selected for negotiation of a potential award. ARPA-H recognizes that this approach may be unfamiliar or new to many proposers and strongly encourages proposers who are interested in a deeper explanation of this approach and how it can be fully utilized by teams to attend the ADVOCATE Proposers' Day and ask any questions they may have.

2.3.3 Data Management and Sharing Plan (DMSP)

Proposers will share deidentified/aggregated data pertaining to processes, performance, and quality collected during the project with other ADVOCATE performers, and potentially, other federal agencies. Open sharing and access to data between TA1 and TA2 performers will be vital to the success of the ADVOCATE program. This agreement will ensure transparency and collaboration within and beyond the program. Proposers must provide detailed plans for handling data storage and computing needs. This includes addressing challenges related to managing and processing the data. These plans may be updated as the program progresses, in concurrence with the ARPA-H program manager (PM). The Data Management and Sharing Plan (DMSP) should adhere to industry-standard data formats to ensure compatibility and ease of integration with ARPA-H and other federal agency platforms. The DMSP should also include strategies for situations where sharing data openly might harm the commercial value of the technology. This includes considering how to protect intellectual property or competitive advantage.

3. Submission Information

Step 1: Submit solution summary.

Submission of a solution summary is required. Proposers to TA1, TA2, and TA3 will either be encouraged or discouraged from submission of a full proposal. *It is **strongly recommended** that only proposers who are encouraged to submit a full proposal do so*.

Step 2: Submit a full proposal.

Only after receiving written solution summary feedback from ARPA-H, encouraging or discouraging the submission of a full proposal, may TA1, TA2, and TA3 proposers submit a full proposal.

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

All solution summaries and full proposals must be submitted via the ARPA-H Solution Submission Portal (https://solutions.arpa-h.gov/). Proposers must register in advance of submissions and registration may take several business days to process. Plan to register well in advance of the solution summary submission deadline as late submissions resulting from delays with registration may not be accepted or considered.

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

3.1 Proprietary Information

Proposers are responsible for identifying proprietary information in any submissions. Submissions containing proprietary information must have the cover page and each page containing such information clearly marked with a label such as "Proprietary."

NOTE: "Confidential" is a classification marking used to control the dissemination of U.S. government national security information as dictated in Executive Order 13526 and should not be used to identify proprietary business information.

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

4. Submission Review and Evaluation Process

4.1 Solution Summary Review Process

ARPA-H will review and respond to all proposers submitting conforming solution summaries. Proposers will receive feedback that either encourages or discourages submission of a full proposal. Regardless of whether the proposer is encouraged to submit a full proposal in response to this ISO, it is eligible to do so after having received its summary feedback. **However, it is strongly recommended that only proposers who are encouraged to submit a full proposal do so** to ensure they do not expend substantial resources developing a full proposal for a solution that does not fit ARPA-H's mission.

4.2 Full Proposal Evaluation Criteria

ARPA-H will conduct a scientific and technical review of full proposals and evaluate based on the four criteria, listed in descending order of importance below. At a minimum, proposers will be provided with notification of the government's decision on whether the proposal was selected for negotiation of an award. Notification of the government's decision will be provided to the primary technical point of contact identified in the proposal.

4.2.1 Criteria 1: Overall Scientific and Technical Merit

The proposed technical approach is innovative, feasible, achievable, and complete. Task descriptions, capabilities showcased and associated technical elements provided are complete and in a logical sequence with all proposed deliverables clearly defined such that an outcome that achieves the goal can be expected as a result of the award. The proposal identifies major technical risks and planned mitigation efforts are clearly defined and feasible. In addition, the evaluation may take into consideration the extent to which the

proposed IP rights structure and software components will potentially impact the ability to commercialize and effectively distribute the technology in a scalable way.

4.2.2 Criteria 2: Proposer's Capabilities and/or Related Experience

The proposed technical team has the expertise and experience to accomplish the proposed tasks; the proposer's prior experience in similar efforts clearly demonstrates an ability to deliver products that meet the proposed technical performance within the proposed budget and schedule; the proposed team has the expertise to manage the cost and schedule and; similar efforts completed/ongoing by the proposer in this area are fully described, including identification of other government or commercial activities where they have led or participated.

The government will assess the qualifications of the key performer team members including the Principal Investigator (PI), Project Manager, AI Engineers, Clinical Integration Experts and any other key personnel on the project team.

For **TA1 Proposers**, preference will be given to teams with multidisciplinary experts in technical, clinical, and commercialization fields who have a proven track record of technical breakthroughs, clinical product development and implementation of AI-based Clinical Decision Support (CDS) and/or DHTs in large health systems.

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

Proposals will be evaluated on the potential future research & development (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 healthcare delivery and the potential to improve health outcomes; the degree to which the proposed project has the potential to transform healthcare delivery; and/or the potential for the project to take an interdisciplinary approach. Further, the proposed solution contemplates the end user and reflects an understanding of the direct needs and benefits for stakeholders whether they are patients, providers, health systems or payers. For example, how would this solution fit inside the clinical workflow? Or how will this be accessible to users in all geographies and at an affordable cost?

4.2.4 Criteria 4: Assessment of Proposed Cost/Price

The proposed cost/price/budget appropriately aligns with the proposed technical solution and reflects an understanding of the resources, schedule, risks, and effort necessary for the project. The proposal also provides sufficient information and/or documentation for ARPA-H to conduct an efficient evaluation of cost/price/budget.

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

4.3 Resource Sharing

Due to the overall goals of the program, offerors are highly encouraged to consider a resource share plan as part of their cost proposal. Resource sharing includes any costs a reasonable entity would incur during ordinary competitive business to carry out the proposed solution that is not directly paid for by the government under the OT or another exiting contract or financial assistance instrument. There are two (2) types of resource-sharing: Cash Contributions or In-Kind Contributions. Cash contributions are the preferred method of fulfilling the performer's resource-share; however, the government will consider in-kind contributions that directly support the proposed solution. Both types are further detailed below:

1. **Cash:** Cash contributions refer to direct monetary payments made by the performer (or third party) to directly support the proposed solution. These contributions include, but are not limited to:

    - Direct financial payments for salaries, supplies, services, equipment purchases, and operational expenses.
    - Funding for the purchase of new laboratory equipment, computers, and software licenses.
    - Payments for external consultants, contractors, travel, and accommodation costs.
    - New Independent Research and Development (IR&D) funds that support research related to the proposed solution and are not recoverable under an indirect expense pool.

2. **In-Kind Contributions:** In-kind contributions refer to non-monetary inputs provided by the performer (or third party) that directly support the proposed solution. These contributions include goods, services, and resources with verifiable market value, and can include:

    - Uncompensated personnel time and effort contributed by project staff.
    - Use of existing laboratory equipment, machinery, and tools not included in any indirect expense pool.

- Supplies and consumables from existing inventories.
- Access to laboratory space, office space, and meeting rooms.
- Analytical and technical services, including data analysis and equipment maintenance.
- Clinical services for trials and patient recruitment.
- Access to proprietary databases, datasets, and research libraries.
- Non-cash licensing of existing IP.

The following are examples of **unacceptable resource-sharing**:

- Sunk costs or costs incurred before the start of the proposed project.
- Resources that were funded by the government under a separate contract or financial assistance vehicle.
- Foregone fees, profits, or other forms of opportunity costs.
- Foregone General & Administrative (G&A) or cost of money applied to a base of IR&D.
- Bid and proposal costs.
- Value claimed for IP or prior research
- Parallel research or investment, i.e., research or other investments that might be related to the proposed project, but which is not directly part of the proposed solution. Typically, this includes activities that would have been undertaken regardless of whether the proposed project is awarded.
- Off-Budget Costs, i.e., costs that will not be risked by the proposer in performance of the proposed project, will not be considered when evaluating resource share.

If resource share is a part of the proposal, please include the following information to substantiate the proposed resource share:

- A Description of each resource share item proposed.
- Proposed Dollar Value of each resource share item proposed; and
- The Valuation Technique used to derive the resource share amounts (e.g., vendor quote, historical cost, labor hours and labor rates, number of trips).

- Supporting documentation that substantiates the valuation technique.

The burden of proof for substantiating resource share requirements is borne by the proposer and any proposed resource share must be annotated in Attachments where indicated. For ADVOCATE performers, the ARPA-H PM's team may also facilitate engagement with investors throughout the duration of the program's period of performance to encourage follow-on funding opportunities for commercialization efforts. **(See Commercialization Roadmap in Appendix E)**

***Fee/profit should not be proposed on efforts that include resource share.**

4.4 Handling of Sensitive Information

It is the intent of ARPA-H to protect all proposals as selection sensitive information and to disclose their contents only for the purpose of evaluation, and only to screened personnel for authorized reasons, in accordance with applicable federal laws and regulations, including the FOIA. Restrictive notices notwithstanding, submissions may be handled by ARPA-H support contractors during the evaluation process for administrative purposes and/or to assist with technical evaluation.

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

4.5 Award General Guidelines

The government reserves the right to select for negotiation all, some, one, or none of the proposals received in response to this ISO. In the event the government desires to award only portions of a proposal, negotiations will commence upon selection notification. The government reserves the right to fund proposals with phases or options for continued work, as applicable.

The government reserves the right to request any additional necessary documentation to support the negotiation and award process. The government reserves the right to remove a proposal from award consideration should the parties fail to reach agreement on award terms, conditions, price, and/or if the proposer fails to provide requested additional information in a timely manner.

In all cases, the government Agreements Officer (AO) will have sole discretion to negotiate all terms and conditions with proposers. ARPA-H will apply publication or other restrictions, as necessary, if it is determined the research resulting from the proposed effort will present a high likelihood of disclosing sensitive information including Personally

Identifiable Information (PII), Protected Health Information (PHI), financial records, proprietary data, any information marked Sensitive, etc. Any award resulting from such a determination will include a requirement for ARPA-H concurrence before publishing any information or results on the effort.

5. General Requirements and Information

5.1 Proposing Teams

It is expected proposals will involve teams with the expertise needed to achieve the goals for the proposed TA(s). Specific content, communications, networking, and team formation are the sole responsibility of the proposer, though ARPA-H will facilitate and stimulate teaming through Proposers' Day. Through the ADVOCATE team website and Proposers' Day, the ARPA-H ADVOCATE team will provide the space and resources to allow TA1 and TA2 potential proposers to develop relationships and learn about other teams technical capabilities and their overall approach.

Proposers must submit a single, integrated proposal led by a PI that addresses all program phases and metrics, as applicable. Investigators may only serve as the lead PI on one proposal submission. Investigators may participate in multiple proposals as a sub-performer/sub-awardee or other appropriate teaming arrangements.

Teams wishing to submit to both TA1 and TA2, must submit separate, technically independent proposals. Proposers can submit two separate proposals: one for the work described in TA1 and another for TA2. If a proposer submits TA1 and TA2 proposals, either one, both, or neither may be selected for negotiations. Technical independence will be determined by the capacity to be integrated with a different TA1 or TA2 partner without the need for a change to the agent.

Proposers interested in submitting a proposal for TA3 cannot submit a proposal for TA1 and TA2. TA3 proposers can only submit one proposal for the TA3 work outlined in this solicitation.

5.2 Health Data Protection and Privacy

- ADVOCATE program deliverables will NOT include raw health data (e.g., names and other identifying information). Performers must de-identify the health data to be included within any program deliverable and implement AI privacy-preserving techniques.
- Sharing of any program information and/or program deliverables will be controlled and in accordance with the negotiated terms of the resulting agreement. Program information will be shared during the period of performance within the ARPA-H

ADVOCATE government team (e.g. the IV&V team and other key government stakeholders).

- The associated IP rights for all program deliverables will be negotiated with each selected performer prior to award. Program information will be controlled in accordance with the agreement, and all ADVOCATE deliverables will be appropriately marked as negotiated by the performer and ARPA- H.

5.3 Scientifically Appropriate Representation in Clinical Study Populations

ARPA-H is committed to healthcare access for all those who need it, where they need it. Therefore, ADVOCATE will ensure that all performers have a clear plan to enroll clinical study populations that aim to match the demographics of the U.S. CVD population.

5.4 Compliance with Regulations Pertaining to Federally-Funded Human Subject Research

Prospective performers clinical studies involving human subjects will need to demonstrate ongoing compliance with all applicable federal, state, and local regulations pertaining to federally-funded human subject research. They will need to obtain and maintain IRB approval and register for a Federal Wide Assurance (FWA).

6. Administrative and National Policy Requirements

6.1 Controlled Unclassified Information (CUI) on Non-Federal Information Systems

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

6.2 Organization Conflicts of Interest (OCI)

The proposer, through submission of a proposal, is required to identify and disclose all facts relevant to any potential OCI involving the proposer, its organization, and/or any proposed team member (i.e. proposed sub-performer). Along with the disclosure, the proposer may be required to submit a mitigation plan, which is a description of the action the proposer has taken to avoid, neutralize, or mitigate the stated OCI. The government may require the proposer to provide additional information to assist the government in evaluating the OCI mitigation plan.

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

6.3 Agency Supplemental OCI Policy

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

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

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

6.4 Research Security Disclosures

Proposals selected for negotiations of a potential award will undergo a Research Security Review (RSR). The RSR involves a review of the proposer's disclosures made as part of the Administrative & National Policy Requirement Document and a validation and comparison of those disclosures utilizing publicly available information and commercially available information tools. Section 10631 of the CHIPS and Science Act of 2022 prohibits federal research agencies, such as ARPA-H, from providing R&D awards on any proposal in which a covered individual is participating in a malign foreign talent recruitment program (MFTRP). It also requires Federal agencies to require recipient entities to prohibit covered individuals participating in MFTRPs from working on projects supported by federal R&D awards.

In accordance with NSPM-33, research organizations should identify and mitigate conflicts of commitment (COCs) and COIs to receive federal funding. COCs and COIs involving foreign countries of concern (FCOCs), including the People's Republic of China, the Russian Federation, the Islamic Republic of Iran, and the Democratic People's Republic of Korea (also known as North Korea), will require risk mitigation plans. A research organization proposing to this ISO must research security disclosures as described in the

Administrative and National Policy Requirement Document and the Office of Science and Technology Policy identified Common Forms. The Common Forms are required for all senior or key personnel.

ARPA-H will conduct an RSR of each proposer and their senior or key personnel **after** a proposal is selected for negotiations of a potential award. The reviews include assessments of potential risks associated with covered individuals' disclosed or undisclosed participation in MFTRPs, funding received from FCOCs, collaboration with FCOC entities (including researchers and research institutions that have been identified on various entity lists), foreign ownership control or influence with regards to FCOCs identified in proposals, and the pursuit of foreign patents stemming from U.S. government funded research prior to obtaining U.S. patent protections. The RSR is not part of the ARPA-H scientific merit review process outlined in this ISO.

If ARPA-H determines the proposer fails to provide all requisite research security disclosures or reasonably provide additional information requested by ARPA-H to assist in evaluating the proposer's disclosures and/or research security mitigations, ARPA-H may remove the proposal from award consideration.

6.5 Intellectual Property

Proposers must provide a good faith representation that the proposer either owns or possesses the appropriate licensing rights to all IP that will be utilized for the proposed effort. ARPA-H strongly encourages IP rights to be aligned with open-source regimes. Further, it is desired that all non-commercial software (including source code), software documentation, and technical data generated and/or developed under the proposed project is provided as a deliverable to the government. IP delivered to the government should align with project or program goals and should be aligned with the level of government funding provided to generate and/or develop the IP.

6.6 Human Subjects Research

A proposal for funding that will involve engagement in human subjects research (HSR) (as defined in 45 CFR § 46) must provide documentation of one or more current Assurance(s) of Compliance with federal regulations for human subjects' protection, including at least a Department of Health and Human Services (HHS), Office of Human Research Protection Federal Wide Assurance. All HSR must be reviewed and approved by an Institutional Review Board (IRB), as applicable under 45 CFR § 46 and/or 21 CFR § 56. The entity's HSR protocol must include a detailed description of the research plan, study population, risks and benefits of study participation, recruitment and consent process, data collection, and data analysis. Performers of ARPA-H funding must comply with all applicable laws, regulations, and policies for ARPA-H funded work. This includes, but is not limited to, laws, regulations, and policies regarding the conduct of HSR, such as the U.S. federal regulations

protecting HSR (e.g., 45 CFR § 46, 21 CFR § 50, § 56, § 312, § 812) and any other equivalent requirements of the applicable jurisdiction.

The informed consent document utilized in HSR funded by ARPA-H must comply with all applicable laws, regulations, and policies, including but not limited to U.S. federal regulations protecting human subjects in research (45 CFR § 46, and, as applicable, 21 CFR § 50). The protocol package submitted to the IRB must contain evidence of completion of appropriate HSR training by all investigators and key personnel who will be involved in the design or conduct of the ARPA-H funded HSR. Funding cannot be used toward HSR until ALL approvals are granted.

6.7 Electronic Invoicing and Payments

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

6.8 Software Component Standards

The health- and healthcare data ecosystem is complex and multi-dimensional with a variety of standards for data models, data transmission protocols, data routing methods, etc. that are similar to and extend the International Standards Organization Open Systems Interconnection Model (OSI). ARPA-H programs are likely to involve research that touches on multiple layers of the OSI model, from low-level radio frequency (RF) based protocols for transmission of data from implantable devices (potentially OSI layers 1-5), to secure and fault tolerant networking protocols for medical devices (potentially OSI layers 3-6), to the exchange of health information including EHR, lab results, and medical images related to a patient between healthcare facilities and health data brokers, including (but not limited to) Health Information Exchanges (HIE) and Trusted Exchange Framework and Common Agreement (TEFCA) Qualified Health Information Networks using protocols such as HL7 FHIR, OSI Layer 7). This diversity requires careful consideration of the most appropriate standards to be used for the specific technologies in development and the layer at which they operate.

ARPA-H is committed to advancing interoperability in today's health ecosystem through the adoption of open, consensus-driven standards and laying the foundation for emerging technologies to interoperate in the health ecosystem of the future through the evolution of these standards across all layers of the health data information technology (IT) ecosystem. With that in mind, we anticipate that the performer will develop software and data communication components that fall into three categories:

1. Components that can leverage today's existing standards without impeding the R&D,
2. Components where extensions to existing standards will be necessary to unlock new capabilities in an interoperable way, and

3. Components in areas where consensus-based standards do not yet exist or where use of standards would seriously limit the ability to efficiently conduct R&D.

Whenever such an existing standard is available that meets the scientific, technical, and research needs of the proposed effort, proposers must use the existing standard instead of creating their own. In cases where an existing standard provides only partial functionality, proposers should expand upon the existing standard, ideally in a way that does not prohibit or interfere with backward compatibility, and create sufficient documentation for the Office of the National Coordinator for Health Information Technology (ONC), and the U.S. Department of HHS agencies or standards organizations, to evaluate extensions for potential inclusion in the standard (including open Application Programming Interfaces (APIs) and open data formats).

In the case of information relating to health- and healthcare data at higher layers of the OSI model, all health IT components should adhere to or (as needed) expand upon applicable national standards adopted by HHS, including the ONC (e.g., FHIR and United States Core Data for Interoperability (USCDI)).

Technical solutions that contain software elements, commercial-friendly open-source licenses (e.g., MIT, BSD, or Apache 2.0) are preferred. If an open, consensus-based standard does not yet exist, the proposer should identify the aspects that lack an open standard, describe a plan to develop a general-purpose open data model and to prototype new open APIs. A strong proposal will explain how the performer will enhance data interoperability (including semantic interoperability) and expand the availability of open, consensus-based standards and data models. If a proposer is unable to develop an open-source solution, please explain why in the proposal.

A proposal must include a technical plan to align with applicable standards based on the OSI layer at which they are operating including (but not limited to) HHS-adopted health IT standards (45 CFR Part 170 Subpart B). For the full description of standards adopted in CFR Part 170, Subpart B, please review the complete text of the regulations; a strong technical solution will also outline integration with the Trusted Exchange Framework and Common Agreement (TEFCA). Adhering to international standard ISO/IEEE 11073 will enable broad support for current and future devices, especially those developed internationally. At other layers of the OSI model, and for software components operating outside the network stack (e.g., health databases, Picture Archiving and Communication Systems (PACS), etc.) other standards will be relevant, and strong technical solutions will seek to utilize or expand upon appropriate open, consensus-based standards.

If a technical solution requires an extension of existing standards or development of technologies outside of the standards, the proposer must schedule a meeting with ARPA-H representatives prior to proposal submission to discuss the deviation to the standards.

6.9 Government-Furnished Property/Equipment/Information

At this time, we do not anticipate any GFP/GFE/GFI will be provided.

6.10 Associate Performer Agreement

To facilitate the open exchange of information, performers will have Associate Performer Agreement (APA) terms included in their award, which requires teams to closely cooperate as an associate performer with other associate performers. It is anticipated that, at a minimum, this will include requirements to:

- Maintain a close working relationship that drives towards ADVOCATE program goals;
- Share information, data, technical knowledge, expertise, resources, inventions, and other IP to the maximum extent practicable in furtherance of ADVOCATE's intended objectives; and
- As deemed necessary by the associate performer, enter into a written agreement with other associate performers setting forth specific procedures related to the foregoing and to memorialize IP sharing arrangements.

This APA requirement will establish a common understanding of expectations to guide the open exchange of ideas and establish a collaborative foundation for the ADVOCATE program. Please refer to Attachment 2, Article XIX - Special Terms and Conditions, Section F for additional information on APA requirements. Please note that ARPA-H is not a party to the APA.