INNOVATIVE SOLUTIONS OPENING (ISO)

CRITICAL ILLNESS IMMUNOLOGICAL REPROGRAMMING AND CONTROL POINT LEARNING ENGINE (CIRCLE)

RESILIENT SYSTEMS OFFICE (RSO)

ADVANCED RESEARCH PROJECTS AGENCY FOR HEALTH

ARPA-H-SOL-26-139
Amendment 1

February 20, 2026

INNOVATIVE SOLUTIONS OPENING (ISO) OVERVIEW INFORMATION

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

TITLE: Critical Illness Immunological Reprogramming and Control Point Learning Engine (CIRCLE)

ANNOUNCEMENT TYPE: ISO, Amendment 1

The purpose of this amendment is to:

- *Change the proposal submission date to Thursday, May 28, 2026.*
- *Replace Office of Commercialization (OC) with ARPA-H.*

All changes are highlighted in yellow.

SOLICITATION NUMBER: ARPA-H-SOL-26-139

Due Dates: (All times listed herein are Eastern Time)

- Proposers' Day: Wednesday, March 11, 2026
  - *For additional details about the CIRCLE Proposers' Day and registration information, please see Special Notice ARPA-H-SN-26-149 at SAM.gov.*
- Solution summary submission: *Monday, March 30, 2026, 1:00 PM*
- Questions & Answers (Q&A) submission: *Friday, May 22, 2026, 1:00 PM*
- Proposal submission: *Thursday, May 28, 2026, 1:00 PM*

NOTE: Proposers are warned that the deadlines outlined herein will be strictly enforced. When planning a response to this notice, proposers should consider that some parts of the submission process may take from one business day to one month to complete.

CONCISE DESCRIPTION OF THE ISO:

The CIRCLE program seeks to create a critical illness Control Point Validation Engine that leads to improvements in intensive care unit (ICU) health outcomes, coupled to reduced stay time and associated costs, by assessing, predicting, and treating immuno-inflammatory dysregulation before it causes organ failure. Critical illness is defined as multiple organ dysfunction requiring specialized medical treatment in an ICU, characterized by acute inflammation and immune dysregulation that propagates rapidly across most tissues, organs, and biofluids and severely impacts quality of life following hospital discharge. Critical illness may be initiated by physical trauma, infectious disease (sepsis), chronic disease (e.g., inflammatory bowel disease, liver cirrhosis, heart disease), stroke, or cancer. Current critical care paradigms are focused predominantly on organ support, with few avenues for the treatment of dysregulated immuno-inflammation. To achieve these aims, the CIRCLE program seeks to obtain targeted near real-time patient data: tissue-specific and system (patient) assessments of critical illness immuno-inflammation biomarkers. These data will be used to define novel control points through validated computational digital twin models of critical illness that will direct personalized immunotherapy. This transformative program will expand our understanding, diagnosis, prognosis, and treatment of critical illness driven by diverse causes, ultimately also impacting chronic disease that is induced or exacerbated by critical illness. Importantly, CIRCLE will involve early integration of clinical translation efforts to accelerate the transition of these innovations to intensivists and their critically ill patients.

ANTICIPATED INDIVIDUAL AWARD: Multiple awards are anticipated.

TYPES OF INSTRUMENTS THAT MAY BE AWARDED: Other Transactions (OTs) awarded under the authority of 42 U.S.C. § 290c(g)(1)(D).

POINTS OF CONTACT (POCS):

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1. PROGRAM INFORMATION

1.1. BACKGROUND

Critical illness is defined[1] as multiple organ dysfunction, characterized and likely driven by dysregulated inflammation and immunity, that ensues from severe infection[2], injury[3] or chronic diseases[4,5]. In the context of critical illness, inflammation spreads and amplifies rapidly across most tissues, organs, and biofluids, which, in turn, can result in multiple organ dysfunction as a primary cause of mortality. Further characteristics include an acute onset (hours to days), long-lasting disease course (a week to months), and sequelae (months to years), concurrent with activation of both innate and adaptive immunity[6]. **Critical illness is thus a self-sustaining process of inflammation leading to cellular stress and damage that causes more inflammation and more damage – a self-propagating vicious cycle.** Furthermore, and seemingly paradoxically, immunosuppression ensues from this over-exuberant inflammation due to the feedback structure that connects inflammation (i.e., innate immunity) with adaptive (i.e., lymphocytic) immunity.

Critical illness affects many facets of society in both developed and developing nations, and with disproportionate impact on the elderly, the young, those without access to healthcare, and the chronically ill[7,8]. Organ dysfunction, accompanied by persistent elevation in circulating markers of inflammation, suppression of immune responses, myocardial and lung fibrosis, and endothelial dysfunction at ICU discharge, leads to long term complications and side effects of invasive and noninvasive resuscitation procedures sometimes referred to as Post-Intensive Care Syndrome (PICS)[9]. A significant number of patients acquire chronic diseases of the affected systems (e.g., kidney disease and diabetes[10]). Thus, critical illness exacerbates chronic diseases, which in turn predispose patients to worse outcomes during and following critical illness[11]. **Recent studies link pre-existing chronic disease burden to immune dysregulation and, in turn, to increased risk of sepsis[12], suggesting the need to take a holistic approach to rational modulation of the immune response in critical illness in order to improve clinical outcomes in broad populations of critically ill patients.**

The current paradigm of diagnosis and treatment of critical illness is phenomenological and fragmented, with different scoring systems[13] used depending on the etiology and proximal causes, all focused on attending to organs as they fail progressively. While this type of fragmentation and imprecision characterizes the state of understanding of many diseases, the need to integrate data and knowledge rapidly for appropriate stratification of critically ill patients is especially acute due to the complexity and heterogeneity of clinical presentation of critical illness, the speed by which this syndrome evolves, and the persistent nature of its sequelae. Currently, diagnosis of critical illness is based on relatively crude scoring systems[14]. Treatment of critically ill patients is focused reactively on organ support, as noted above. Despite the incremental reduction of critical illness mortality through the slow evolution of protocolized procedures related to organ support, critical care still fails to address the underlying causes of the disease. Perhaps for this reason, the health of ICU survivors is often impaired long after hospital discharge, with patients suffering increased mortality and reduced productivity associated with persistent immune dysregulation post-hospitalization. Recent years have seen a multitude of studies aimed at defining critical illness endotypes[15,16] but the purely data-driven approaches that underlie these machine learning (ML)-based

segregation approaches are not well-suited to and have not been used to discover novel therapeutic modalities for critical illness. **Thus, the state of critical care is dire despite incremental improvements in organ support and diagnostic capabilities,[17,18] as there are currently no Food and Drug Administration (FDA)-approved drugs that treat the proximal causes of critical illness other than broad-spectrum antibiotics (which only impact those patients undergoing critical illness due to bacterial infections), corticosteroids (which at best help 20-30% of patients[19]), and anti-interleukin-6 (which is of similarly limited utility[20]). The perception of intractability of critical illness is reflected in very limited investment in new interventions[21,22] and few advances in our ability to provide personalized, targeted treatments.**

To break through the current stagnation in the field of critical care and reduce the significant cost and health impacts of critical illness, there is an urgent need to rethink the current reactive paradigm based on the treatment of failing organs. Instead, we propose the need to assess, predict, and modulate the underlying mechanisms of immune dysfunction, involving dynamic, pathophysiologic, immune-related networks[23]. CIRCLE seeks to usher in a new stage of treatment for critical illness, not only through the development of new science, but through aggressive testing of capabilities that affect treatment pathways explored in the clinic. Although patients in the ICU are monitored extensively for vital signs and specific indicators of organ dysfunction that can be assessed relatively easily in the systemic circulation, the technology for rapid, near-real time monitoring of tissue-specific immune biomarkers is still in its infancy. Knowledge of specific indicators and drivers of critical illness progression, the mechanisms involved in these pathways, and the critical control points[24] that could be modulated therapeutically to combat disease progression is lacking.

1.2. NATIONAL HEALTH IMPACT

Over 7 million Americans are treated in ICUs every year[25], with average stays of 3.5 days[26]. 70-80% of ICU patients fit the definition of being critically ill[27], and these patients represent the overwhelming fraction of the time spent in the ICU and the associated costs. The length of ICU stay is highly variable, with some patients requiring more than three weeks before being well enough to transition to non-ICU hospital rooms. Costing more than $3000/day[28], this amounts to over $70 billion of annual health care costs. Actual costs may be much higher in cases in which equipment such as mechanical ventilators or renal dialysis machines are needed for extended periods. Notably, the in-hospital costs alone for chronic critically ill patients are over $20 billion per year[29]. The true monetary impact of critical illness is likely far higher, considering the number of people that die in the ICU (10%); the significant in-hospital and outpatient care that is needed after exiting the ICU; and that fact that many patients undergo extended "chronic critical illness"[30] and can contract or exacerbate lifelong chronic diseases such as diabetes and kidney disease post-critical illness. Pre-existing chronic diseases of the gut, kidney, liver, heart, and lung can result in poorly understood complications necessitating ICU care, and all are serious risk factors for poor outcomes in and after the ICU[31]. In addition, ICU capacity has little room to buffer unexpected disturbances; under non-emergency health care conditions, American ICU beds are 68% occupied[32], leaving little room for emergency surge capacity.

1.3. PROGRAM SCOPE

The goal of the CIRCLE program is to reduce time in the ICU due to any of the major causes of critical illness, since doing so will lead to reduced downstream morbidity, mortality, and cost. This goal will be achieved through rapid and comprehensive assessments of patient immuno-inflammatory biomarkers. These data will inform dynamic, mechanistic, patient-specific computational models (digital twins) capable of identifying control points at which precise modulation can effect a rapid return to health, leveraging and integrating into existing clinical workflows to the greatest extent possible. The CIRCLE program thus aims to develop novel diagnostic modalities that will be used to personalize disease assessment via patient-specific digital twin modeling, which in turn will guide the precise administration of existing immunomodulatory modalities in the ICU to improve the lives of critically ill patients.

CIRCLE-sponsored research efforts may leverage studies of specific subpopulations of critically ill patients but must be directed towards defining and modulating commonalities in tissue-specific immune dysregulation across the spectrum of this disease syndrome.

Accordingly, research within the CIRCLE program is expected to encompass and integrate advances in detection of biomarkers indicating the status, dynamics, and organ/tissue-level variation of the immune system; mechanistic computational modeling of the immune system based on individualized patient data (digital twins); and therapeutic decision support based on those data and models. CIRCLE will focus initially on repurposing FDA-approved therapies that can effect immuno-inflammatory reprogramming, ideally with tissue-specific precision. If justified, CIRCLE will support the development of novel immune-modulating approaches as a means of validating specific predictions derived from digital twin models and/or as novel therapeutics. To achieve this goal most optimally, CIRCLE expects performers to be integrated, multi-component teams with expertise in clinical care of critically ill patients (e.g., neuro-ICU, trauma ICU, burn care units, surgical critical care units, pulmonary, nephrology, and cardiology critical care units, extracorporeal membrane oxygenation (ECMO) units, etc.), animal models of critical illness, data platforms, computational modeling, and the specific intervention modalities on which the team will focus. Performer teams may include academic institutions, not-for-profits, corporate entities, or a combination thereof.

The following are out of scope for the CIRCLE program: Efforts whose entire scope is relevant to only one specific cause of critical illness, e.g., sepsis. Efforts that focus solely on elimination or early detection of infectious agents and could not be generalized to address non-infectious causes of critical illness would be out of scope for the CIRCLE program. Efforts that base all their digital twin modeling work solely on ML techniques to perform patient stratification will be considered out of scope. The primary focus of the CIRCLE program is on critical illness in adults. Due to the differences in the immuno-inflammatory mechanisms between adults and neonates or pediatric populations as well as the difficulty in obtaining sufficient data in these groups, proposers are strongly encouraged to focus on adult populations to strengthen the generalizability if CIRCLE therapeutic targets.

1.4. PROGRAM DESCRIPTION

CIRCLE will develop the ability to sense, model, and directly affect the immuno-inflammatory processes that lead to progressive organ dysfunction, thereby reprogramming the feedback loops of inflammation and the progression of cellular stress and damage. Upon conclusion, work carried out by CIRCLE performers will help reduce length of time and resource utilization as compared to current ICU care. Ultimately, these improvements are expected to result in improved clinical outcomes for critically ill patients, as well as cost savings. The CIRCLE program is therefore soliciting transformational proposals that shift the focus from reactive care of failing organs towards addressing the underlying immune dysfunction. CIRCLE-sponsored diagnostic/modeling/therapeutic systems will work in concert with existing, protocolized, organ-supportive care, allowing intensivists and ICU staff to monitor the state of the immune system in near real time, gaining crucial, tactical, and spatiotemporal insights regarding where, how, and when immuno-inflammatory processes are diverging from healthy trajectories. The diagnostic and modeling platforms developed under CIRCLE will provide technologies for reprogramming computationally defined immune feedback loops that drive critical illness pathophysiology. **Overall, CIRCLE will improve patient trajectories in the ICU, giving a rational basis and operational means for stepping critically ill patients down to general hospital beds sooner (with a target of a 25% reduction in average ICU stay length), reduce readmission to the ICU, and improve post-hospitalization outcomes while also reducing costs.** Throughout the period of performance, CIRCLE performers will work towards the integrated development of clinically viable, practical systems for diagnosis, prognosis, and clinically effective therapeutic interventions that will progress towards FDA approvals and clinical adoption. To support this endeavor, performers will be able to access ARPA-H-provided resources to aid the process of regulatory approval and commercial transition of their systems.

CIRCLE will bring together integrated technical area (TA) performer teams that will develop this capability, as follows:

CIRCLE performers will create and compile datasets and methods for biological sampling from patients that represent the spatiotemporal variation of biomarkers relevant to immuno-inflammatory processes that underlie critical illness. Proposers should focus on obtaining and generating data that support mechanistic modeling of the underlying immune, inflammatory, and cellular stress/damage processes that characterize critical illness as appropriate for generating, calibrating, verifying, and validating companion digital twin simulations. To the greatest extent practical, data should come from patients as opposed to animal models (although the use of clinically realistic animal models for verification and validation of model predictions, for the evaluation of therapeutics, and the safety and effectiveness of new sampling methods is appropriate, as are data obtained from other experimental systems if justified). Proposers will identify existing data sets that can be leveraged and will propose methods for expanding and improving data resources, particularly in the areas of temporal and spatial resolution. Datasets may be used for stratification of subpopulation of critically ill patients, but the expectation is that the data

should focus on mechanisms common to critical illness and be broadly relevant and applicable to critical illness of diverse proximal causes. To this end, performers will be expected to work with ARPA-H resources that will both provide access to large-scale patient data and will also incorporate performer-generated data into a common CIRCLE database that will ultimately become a public resource. Performers will establish data generation and collection methods that will work efficiently in the clinical setting to support the complete CIRCLE measure-model-modulate triad. These methods must facilitate rapid and frequent data acquisition sufficient to track the progression of immuno-inflammation across relevant tissues over time frames relevant for the digital twin models, and, if justified, effective clinical decision making.

CIRCLE performers will develop and validate computational "digital twin" models of critical illness pathophysiology capable of predicting individual critical illness trajectories and serving as the basis for both novel diagnostics and defining novel immune system control points. These digital twins should incorporate individualized, dynamic, tissue-specific patient data. These models will be capable of describing and predicting the disease trajectories of individual patients as well as patient sub-populations, explain underlying pathophysiologic processes, suggest therapeutic control points that can be leveraged to treat individual and subgroup manifestations of critical illness, and be capable of serving as the basis for simulated (*in silico*) clinical trials of putative therapies. *In silico* clinical trials are a use of computational modeling to predict how treatments interact with the human body. Simulations are not expected to substitute for real-world clinical trials. However, *in silico* trials can be used as a cost- and time-efficient way to make pre-trial predictions, inform the design of clinical trial protocols and inclusion/exclusion criteria, optimize dosages and treatment schedules, assess safety, and, through the use of virtual populations with varying genetics, health backgrounds, and presenting etiologies, enable mechanistic insights into disease processes, and the possibilities for personalized care. Proposers should describe how mechanistic digital twin models of critical illness will be constructed based on (and calibrated to) the anticipated data types, number of biomarkers (or amount of information) to be assayed, sampling frequency, spatial resolution, and data set size. Proposers should indicate the type of modeling and analytics that will be applied to extract key factors, control points, and/or mechanistic insights that will result in decision support for precision repurposing of existing, FDA-approved therapies as well as the development of novel therapies. To the greatest extent possible and ideally at the initiation of funding, computational models should be sufficiently developed so as to be capable of reproducing distributions of data found not only in the specific biomarker data streams developed by the performer but also in retrospective biological data of critical illness, patient data from electronic health records, and real-time data from standard ICU instrumentation. Models should be capable of generating simulations, both of patient populations and potential courses of treatment, to enhance the process of evaluating therapeutic interventions (i.e., *in silico* clinical trials). Models developed under the CIRCLE program are ultimately expected to be compatible with FDA-compliant platforms for evaluation, and ideally generalizable to additional data types and biomarkers beyond those chosen by the performer; ARPA-H resources will support this aspect of the work. If justified,

these digital twin models could be augmented by appropriate ML approaches for integration of new data or for other purposes.

CIRCLE performers will focus initially on repurposing existing, FDA-approved therapies that can effect immuno-inflammatory reprogramming, ideally with tissue-specific precision, based on individualized patient data and computational models of immune system dynamics and their generative mechanisms. If justified, TA3 will support the development of novel immune-modulating approaches as a means of validating specific predictions derived from digital twin models and/or as novel therapeutics. Proposers should focus on interventions that will modulate or reprogram the immune system or other critical illness-associated pathways that will interrupt or diminish the progression of inflammatory processes and cellular stress/damage that are the hallmarks of the condition. Therapeutic interventions should be integrated with, and based on, the data obtained at the bedside and analyzed and interpreted by the computational digital twin models developed within the program. Interventions must be timely and responsive to individualized and case-specific data, incorporating knowledge of the spatial location (organ and tissue origin) of inflammatory processes, as well as the dynamics of critical illness in individual patients. Proposed interventions should be tested under the most patient-realistic conditions practical, whether in simulations, large animal/non-human primate trials, and/or human studies. To the greatest extent possible, both efficacy and safety data from pre-clinical and clinical studies should be incorporated into the databases made available for all CIRCLE performers, as well as FDA-compliant models made available through ARPA-H. CIRCLE performers will be afforded the opportunity to utilize ARPA-H resources to leverage clinical trial consortia to accelerate the process of obtaining FDA approvals for novel therapies.

1.5. TECHNICAL COMPONENTS

The CIRCLE program will achieve its goal of reducing the amount of time patients spend in the ICU and improve outcomes through innovations in systems immunology approaches to critical illness. CIRCLE will be composed of several integrated TA performer teams conducting research & development (R&D) to achieve the desired Measure-Model-Modulate approach to critical illness care. TA performer teams will include a Team Integrator component (Section 1.5.1, below) to manage the integration of the three TAs of the CIRCLE program (measurement, modeling and modulation) into systems capable of working and being adopted into practice in ICUs.

CIRCLE TA performer teams will integrate the following three components to achieve effective therapeutic systems. Detailed biomarker data from patients, models of the relevant physiological systems, and interventions that modulate critical factors, will help reprogram the immune response to control runaway immuno-inflammation and block further cellular stress/damage, as follows:

- **TA1: Measure - Dynamic Immune Descriptor:** Measurement of systemic and tissue-associated immune status biomarker dynamics appropriate for the development of models (TA2) and therapies (TA3). Acquisition of complementary datasets. Incorporation of project data into common program database.

- **TA2: Model - Digital Twin Generator:** Modeling of critical illness systems and control points appropriate to available data (from TA1). Tissue-attributed and time-series data will enable increasingly powerful artificial intelligence (AI) models of critical illness overall and of key control points that can be targeted to mitigate or reverse its progression. Incorporation of models into FDA-compliant model testing platforms.
- **TA3: Modulate - Rational Immune Reprogrammer:** Digital twin-guided rational modulation of critical illness inflammation and immunity. Testing of immunomodulatory interventions in the context of critical illness will create increasingly useful datasets for learning and development of future computational models.

TA performer teams' efforts will be augmented by separate performer teams that will provide resources and advice to accelerate progress towards program goals, as well as independent validation and verification (IV&V). **These IV&V groups will be designated individually as "Acceleration Platforms (APs)" (see sections 1.5.3 and 1.6.4).** AP teams are charged with developing a collection of resources to ensure data access, interoperability, model validation, regulatory compliance, and access to adaptive clinical trials.

Thus, CIRCLE will be composed of two types of performers: 1) integrated teams each working on all three TAs, and 2) no more than three performers carrying out support and Independent Verification and Validation (IV&V) roles in three separate "APs" (AP1, AP2 and AP3) that are paired with the corresponding TAs: TA1, TA2 and TA3 (See Figure 1 and sections 1.5.2 and 1.6.4 below).

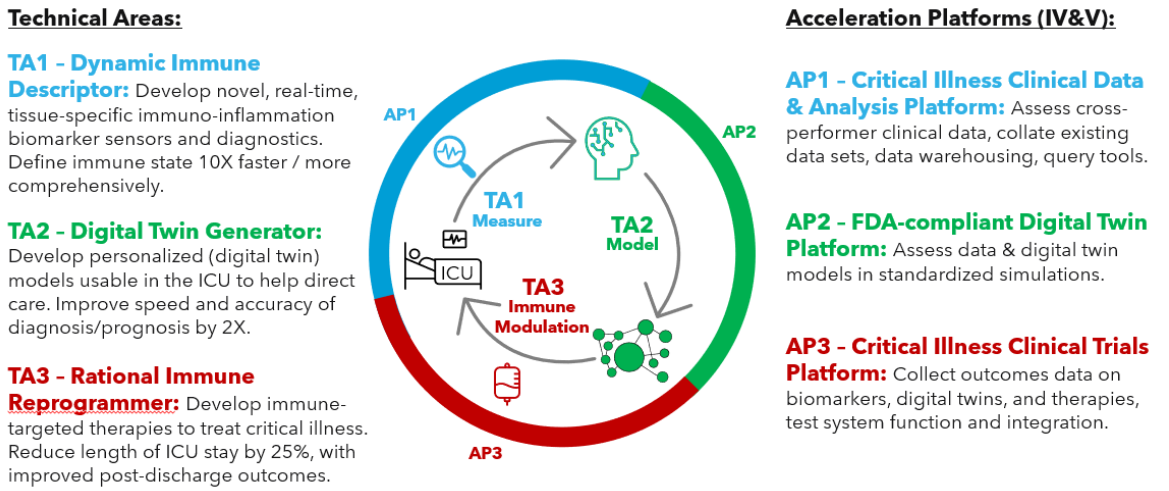

Figure 1. CIRCLE Program TA scheme and paired IV&V AP descriptions – APs support work across all TA performers

1.5.1. Team Integrator

Each TA performer team will be composed of three sub-groups addressing the "Measure" (TA1), "Model" (TA2), and "Modulate" (TA3), TAs of the CIRCLE program, to be integrated, coordinated, and managed by the Team Integrator component of that team. The Team Integrator component of the CIRCLE program represents and highlights the overarching focus on **integrated delivery of both research & development as well as**

commercialization/transition inherent to the CIRCLE program; this component is expected to play a management role and thus **must be led by the performing teams' Program Leads (PLs)**. The Team Integrator component is responsible for assuring that all team-level milestones (section 1.6.2) are met. Areas of responsibility include:

- **Within-team, cross-TA integration, and technology transition**: The Team Integrator will assure that data collection under TA1 will deliver the data needed (in terms of scope, volume, accuracy, frequency/granularity, and volume) to achieve the needs of TA2 and TA3, and that TA2 develops models that will deliver the information needed by TA3 to deliver effective therapies. Team Integrators will identify TA-specific technologies and multi-TA integrations that may transition to the commercial marketplace and support the transition of integrated healthcare innovations. Transition-related activities are likely to include additional pre-clinical and clinical studies as preparation for regulatory submissions for diagnostic, software as a medical device (SaMD), and therapeutic platform(s) based on repurposed FDA-approved (or novel) therapeutic modalities. Team Integrators will engage with startups or other commercial entities to bring technology to the marketplace, produce studies supporting the cost proposition, breadth of consumer applicability, and usability, etc. Progress towards transition will be assessed semi-annually by a panel of external experts (see section 1.6.3) and aided by ARPA-H (see section 1.6.5); the Team Integrator will play a central role in presentations to that panel and will be responsible for acting on the panels' feedback.

- **Program-wide TA integration and interaction with AP teams:** Team Integrators will collaborate with the AP teams to reach consensus on the choice of data to be collected by the AP1 team. Similarly, Team Integrators will work to assure that the TA groups take advantage of common data products provided by the AP1 performer. Team Integrators will collaborate with the AP2 performer to incorporate TA2-generated models into standardized CIRCLE digital twin platform(s) for validation and future FDA evaluation. The team integrator will additionally assure coordination with AP2 and AP3 for validation and improvement of digital twin models based on trials data. Team Integrators should leverage access to platform trials that will be made available through interaction with the AP3 performer.

1.5.2. Technical Areas (TAs)

TA1: Dynamic Immune Descriptor:

The TA1 component of CIRCLE will obtain data that can support the detailed modeling of patients' immune state to be carried out by TA2, and the immune reprogramming interventions to be carried out by TA3. As critical illness is a syndrome characterized by rapid, dynamic alteration of the immune system propagating across organs and tissues, TA1 must focus on rapid (and rapidly repeated) measurements that are tissue-/organ-localizable while also providing information at the systemic, whole-patient level and capturing both the progression and resolution of critical illness within the ICU time frame.

- **TA1.1 (Preparation) focuses on defining the detailed milestones and metrics of the program.** Milestones and associated TA1 specific and project-wide metrics are

detailed in section 1.6.2, below. Performers will collaborate with the AP groups (section 1.6.4) and the ARPA-H Program Manager to define project-wide targets and baselines.

- **TA1.2 (Research) focuses on research into innovative and streamlined methods for obtaining new rapid and localized data tailored to the proposed modeling under TA2 and reprogramming interventions under TA3.** Research will establish the methods that will be employed for improving the speed and effectiveness of collecting immune and related biomarker data. Initially, in Phase I of the program, performers will obtain as wide a range of biomarkers as possible so that analytical methods developed under TA2 can identify the minimal subset of biomarkers sufficient to define clinically relevant immune states in the trajectory of critical illness to inform therapeutic interventions under TA3. Performers will demonstrate how their methods will enable rapid sampling and read-out of biomarker levels; the expected speed, accuracy, and precision of the methods; and strategies for assessing the biomarker levels in both the systemic circulation and in source tissues or organs. Performers may focus on specific sub-populations of critically ill patients for data collection if that is part of the overall strategy to address critical illness more broadly.
- **TA1.3 (Development) focuses on transition of the research-grade detector/bioassay systems into ones capable of clinical use and scaled-up production and deployment, utilizing a down-selected subset of key biomarkers that have been identified during the research phase.** Systems (diagnostic platforms) will be capable of sufficient end-to-end speed, repeat usage, and/or be sufficiently low-cost to be one-shot and disposable, to generate data over the course of a typical ICU stay. They will produce readouts of data sufficiently fast for clinicians to react (directing timed, targeted, and properly dosed care) considering the typical rate of change in patient immuno-inflammatory state during episodes of critical illness. Performers will iterate plans that will achieve the necessary development through the several Phases of the program, in conjunction with AP performers.

TA2: Digital Twin Generator

The TA2 component of CIRCLE will model the immune system of patients suffering from critical illness utilizing data from TA1, and providing detailed, actionable information to enable the immune reprogramming interventions to be carried out under TA3. Personalized computational models (Digital Twins) must be able to incorporate data on the changing immuno-inflammatory state as well as relevant information about an individual patient's medical history and/or relevant data streams obtainable in the ICU. These models must go beyond pattern-based patient stratification but rather must incorporate some aspect of biological mechanism suitable for identifying therapeutic control points and allowing simulation of the effects of possible interventions.

- **TA2.1 (Preparation) focuses on defining the detailed milestones and metrics of the program.** Milestones and associated TA2 specific and project-wide metrics are detailed in section 1.6.3, below. Performers will collaborate with the AP groups (section 1.6.4) and the ARPA-H Program Manager to define project-wide targets and baselines.

- **TA2.2 (Research) focuses on research to create, calibrate, and optimize models that are able to stratify patients, discover control points in the progression of and recovery from critical illness, simulate the effects of immune-modulating therapies, and create simulated (*in silico*) digital trials of CIRCLE-derived technologies.** Performers in Phase I will incorporate data sets with the necessary volume and spatiotemporal granularity to train the proposed models, either from preliminary work, from external sources, or obtained from the CIRCLE program database in collaboration with AP1 (see section 1.6.4). The frequency of data collection, and the accuracy of point-of-origin determinations will be sufficient to generate predictions of patient trajectories, control points and the effects of control point modulations. Performers will apply analytical methods suitable for extraction of these outputs while incorporating quality control of digital twin models in describing both healthy and critically ill states.
- **TA2.3 (Development) focuses on the process by which research-level models will be streamlined, enhanced, and validated to enable both diagnostic use in the ICU environment by clinicians (to support individualized critical illness therapy decisions) as well as in the context of simulated (*in silico*) clinical trials to assess potential therapeutic regimens (therapeutic target, patient selection, dosage, and timing).** Performers will generate "pivotal" *in silico* trials (i.e., non-exploratory simulations, potentially ready for real-world implementation as a Phase II or Phase III clinical trial) to establish the likelihood that modulation of indicated control points would have a beneficial effect on critically ill patients. This should include, specifically, predicted reductions in ICU length of stay and concomitant biomarker profiles indicative of this reduction. Performers must establish parameters for those interventions including patient stratification, timing of interventions, and required degree of target activity modulation. Performers will achieve the necessary development through the distinct Phases of the program and will work with Acceleration Partner teams to ensure that digital twin models are robust and can support regulatory filings.

TA3: Rational Immune Reprogrammer

The TA3 component of CIRCLE will test approaches to treating critical illness that utilize the data obtained under TA1 combined with the outputs of the digital twin models developed under TA2 to modulate key control points in the critical illness disease process, thereby enabling physicians to improve patient outcomes allowing for faster step-down from the ICU versus current standard of care. Performers will test the efficacy and safety of these therapeutic interventions in a setting that will produce results suitable for an initial submission to the FDA.

- **TA3.1 (Preparation) focuses on defining the detailed milestones and metrics of the program.** Milestones and associated TA3 specific and project-wide metrics are detailed in section 1.6.3, below. Performers will collaborate with the AP groups (section 1.6.4) and the ARPA-H Program Manager to define project-wide targets and baselines.

- **TA3.2 (Research) focuses on research into intervention methods.** Therapeutic methods must incorporate the output of digital twin models and must target model-identified control points for modulation. Performers will focus initially on the (re)use of FDA-approved therapies. Where appropriate and justified, performer teams can validate TA2 model predictions using existing or novel compounds, devices, or methods that are not FDA-approved. If novel therapeutic approaches are used as a means of validating model predictions, performers will clearly establish the feasibility of the methods for testing their effectiveness and specificity for the desired target(s) through appropriate *in vitro*, *ex vivo*/micro-physiological devices, and/or animal studies.
- **TA3.3 (Development) focuses on carrying out clinical studies to establish the feasibility, safety, and potential efficacy of therapeutic interventions.** Performers will carry out pilot clinical studies in conjunction with Acceleration Partner teams to utilize digital twin model information on the timing and dosage of modulating interventions to establish protocols for pilot clinical studies. To complete the cycle of model refinement inherent in the CIRCLE program, data from all TA3 studies will be deposited in the CIRCLE database to be utilized for improvement of TA2 models (see section 1.6.3). In conjunction with TA2 simulation studies, performers will carry out studies with Acceleration Partner teams to validate the proposition that the interventions will result in at least a 25% reduction in the time patients spend in the ICU before transfer to step-down units or other non-ICU care. In the case of non-FDA approved therapies, TA3 performers may engage in activities advancing novel therapeutics to the pre-IND (investigational new drug/device) stage such as (for drugs): pharmacokinetics, pharmacodynamics, ADME (absorption, distribution, metabolism and excretion), toxicology, CMC (chemistry, manufacturing and controls), and (for devices): biocompatibility, safety, human factors, usability, etc., as well as relevant regulatory approaches following approval by the Program Manager.

1.5.3. Acceleration Platform (AP)

In the CIRCLE program three AP performer teams will both augment the efforts of the TA teams as well as carry out IV&V duties in addition to providing direct support of the TA. These support efforts are discussed briefly here, and in detail in section 1.6.4, below.

- **AP1: Critical Illness Clinical Data & Analysis Platform:** The AP1 performer will collect data and provide analytical tools (data products) that will constitute a shared resource for all TA performer teams. These data will be drawn from public and private sources as well as the data generated by the TA performer teams themselves.
- **AP2: FDA-compliant Digital Twin Platform:** The AP2 performer will establish a system for all TA performers to test and evaluate their Digital Twin models using common test data and standardized systems both for the purpose of performance optimization and as a bridge to obtaining FDA approvals.
- **AP3: Critical Illness Clinical Trials Platform:** The AP3 performer will provide planning, guidance and access to resources and facilities to enable and accelerate validation studies for all TA performers. This will include support of clinical (human) studies.

Additionally, the AP3 performer will assist with the testing of prototypes in ICU environments and with ICU systems and workflows.

1.6. PROGRAM STRUCTURE

CIRCLE is a 5-year, 3-phase program that consists of three TAs, and three TA-associated APs as components of a distributed technical augmentation and IV&V team. These components will work together to develop, test, and integrate innovative means of assessing dynamic immune state, computational modeling, and modulation of the immune system to mitigate critical illness. Taken as a whole, CIRCLE will lead to the creation of technologies, processes and methods that can transition into the clinic and healthcare marketplace efficiently and sustainably. CIRCLE will structure work across three Phases, as follows:

- **Phase I (3 years, months 1-36):** Performers will develop, prototype, evaluate, and test their approaches in each of the three TAs. TA1 will collect sufficient data to enable TA2 to create the models needed to identify control points suitable for clinical decision support. TA3 will design and perform control point modulation experiments to validate those predictions from the TA2 models and predict the impact of existing and hypothetical therapies. Working in concert with the associated AP performers, the TA1 component will ensure that their data acquisition approaches are interoperable across the TAs and with systems that will allow seamless integration into clinical practice. By the end of Phase I, plans and approvals (i.e., Institutional Review Board (IRB) approvals) must be in place for the testing to be carried out in Phase II. Similarly, initial outreach and planning for FDA submissions and approvals must have taken place.
- **Phase II (option, 1 year, months 37-48):** Performers will engage in a process of *in silico* and initial clinical evaluation to test and refine the integrated measurement, modeling and modulation systems. Validation of computational model simulations and predictions may involve either animal models or human subjects, or both. Performers will engage with transition partners and develop transition plans related to any of the potential final products that the performer team will produce (an integrated system and/or innovations specific to TA1, TA2, and/or TA3). The performer is required to secure at least 5% of their Phase II budget in funding from commercialization partners in Phase II.
- **Phase III (option, 1 year, months 49-60):** Performers will engage in pre-transition activities including: business planning, fundraising, developing partnerships, obtaining initial FDA classification and making appropriate filings, engaging in clinical trials, refinement of devices, processes, and systems integration, user testing, etc. These activities should focus on transition towards commercialization of any products derived from TA1, TA2, and/or TA3. As such, by the end of Phase III it is expected that performer teams will have completed the necessary steps for a regulatory filing on at least one product capable of improving diagnosis and/or treatment of critical illness. The performer is required to secure at least 25% of their Phase III budget in funding from commercialization partners in Phase III.

Progression to Phase II and to Phase III will depend on performance against milestones (Table 1), metrics (Table 2), and evaluation by the AP IV&V performer(s). At the end of Phase I, a down-select may occur. These milestones and metrics are designed to evaluate not only

technological aspects of the work (completeness, integration, accuracy, efficiency, reliability, practicality, safety, cost), but also the progress towards transition (planning, partnerships, usability, acceptability).

1.6.1. Proposal Scope

Each proposal responsive to this ISO may be of one of two types: they must either address all three TAs, "Type A", or address a single AP component, "Type B". CIRCLE is seeking a diversity of approaches for each TA, and therefore individuals and corporate units may not contribute to more than one Type A proposal. Additionally, to avoid conflicts of interest between TA performers and AP performers, no organization, whether acting as a primary or sub-performer, may participate in both a Type A and a Type B proposal.

- **Technical Area (TA) Proposals (Type A):**

  Proposals must address all three TAs. The proposing organization must designate an individual or individuals (typically the proposal Program Lead (PL) working with one or more administrative managers) to have the primary role of Team Integrator to coordinate the activities of groups dedicated to the three TAs, and assure that milestones are met and deliverables delivered, whether these groups are components of the proposing organization or sub-performers. All proposals must include appropriate effort on the part of the PL to coordinate each TA with AP/IV&V partners (AP1, AP2, and AP3) as indicated in sections 1.6.3, and 1.6.4 below.

  Multiple awards are anticipated for TA team (Type A) performers to assure sufficient diversity in measurement, modeling, and therapeutic modulation, as well as a diversity of different etiologies of critical illness from different hospitals and regions to foster a variety of solutions that reflect the U.S. healthcare system.

  Regardless of the specific technological approaches included, Type A proposals are expected to address the following overarching goals:

  - Monitoring key, dynamic aspects of immuno-inflammatory status of patients sufficiently quickly and at a sufficient granularity to detect clinically relevant changes in the course of critical illness, and with an ability to discern (directly or indirectly) both systemic and organ/tissue-level source(s) of dysregulated immuno-inflammation
  - Incorporating data into a widely usable database useful for computational modeling
  - Creating updateable, patient-specific computational models (digital twins) capable of 1) representing and predicting the individualized course of critical illness status; 2) suggesting and evaluating therapeutic options based on molecular, cellular, and tissue-based mechanisms (clinical decision support; and 3) predicting the patient-specific therapeutic impact of these options
  - Providing a computational platform for defining therapeutic control strategies for dysregulated immuno-inflammation, which can serve to guide both *in silico*

and real-world clinical trials by providing patient inclusion/exclusion criteria, therapeutic dosage and timing recommendations, and impact of therapies on key clinical outcomes

- Advancing the state of the art of precision immunotherapy for critical illness with the goal of reducing the time spent in the ICU and improving in-hospital patient outcomes.

- Assessing the anticipated return on investment of the proposed work, estimating clinical benefits (e.g., reductions in ICU length of stay, morbidity, and mortality) as well as the economic impacts on the cost of care and potential benefits to patients, clinicians, and hospitals.

Assessment of post-hospitalization, longer-term outcomes is not directly in-scope under CIRCLE, but any studies that follow patient populations post-hospitalization will be viewed favorably if they comply with the other criteria described above.

Proposals are expected to include effort from individuals with all the relevant expertise to achieve the proposed goals of each of the TAs. **Proposers must submit a single proposal led by one PL under a single prime performer that addresses all program Phases and TAs.** Phases II and III are options to be exercised by the government and may require the negotiation of an updated task description document (TDD). We anticipate that progression to Phase II will involve a down-select.

- **Acceleration Platform (AP) Proposals (Type B):**

  AP performers are considered distinct from proposers applying to serve on the main CIRCLE program. Acceleration Partner proposals may only address one of the three IV&V AP areas (AP1, AP2, or AP3). Proposers may submit distinct proposals for more than one AP area.

  AP proposals must include plans, effort allocation, expertise, materials, and equipment necessary to achieve the individual tasks indicated in section 1.6.4 for that specific AP. Similarly, each AP proposal must include the same elements for reporting the results of those tasks to the Program Manager to assist in evaluation of the progress of the TA performers towards the indicated milestones.

  A single award is expected for each of the three AP areas. **Proposers must submit a single proposal led by one PL under a single prime performer that addresses all program Phases and a single AP.** The inclusion of sub-performers within AP teams under a prime is acceptable if needed to address all the goals of that AP. Phases II and III are options to be exercised by the government and may require the negotiation of an updated TDD.

1.6.2. Program Milestones & Metrics

CIRCLE's milestones (Table 1) focus on establishing the capabilities for a future in-ICU system to assess and treat the underlying immuno-inflammation driving critical illness and stress the coordination between TAs and AP groups to validate discoveries and drive towards

commercial transition. A complete list of milestones, listed chronologically, with more detailed description can be found in the Appendix.

Meetings and required travel – An in-person kickoff meeting will be held soon after the performers' period of performance start date (see section 6.5). Additionally, an annual in-person meeting will be held in each of the 5 years of the program. Proposers should plan for 2-day events at which, at the very minimum, the Project Lead (PL) and leads for each TA are expected to attend. All other program meetings will be held online.

*Table 1: Milestones Table**

	Milestone	*Deadline (from Award Date)*
All Performers	Attend Kickoff meeting	TBD
	All TAs and APs, collaboratively establish metric methods, baselines and targets	3 months
	All TAs and APs, all Associate Performer Agreements (APAs) must be complete and in effect	3 months
Each TA	Establish/finalize research plans, obtain any needed approvals for protocols	6 months
	Meet all metrics targets	1, 2, 3, 4, 5 years
	Perform component level evaluation of technology in an ICU-like environment	4 years
	Perform integrated system evaluation of technology in an ICU-like environment	5 years
TA1	Establish a minimal and sufficient set of biomarkers that can be assessed with necessary frequency and spatial resolution (as required by TA2 model specifications)	1 year
	Demonstrate tractable and reproducible assessment (with frequency and localization metrics met) of a set of immuno-inflammatory biomarkers sufficient for calibration of TA2 digital twin models and relevant to TA3 modulation.	1.25 years
	Assess 25%, 50%, 75%, 100% of planned samples	1, 2, 3, 4 years
TA2	Establish digital twin architecture & ML methods (in collaboration with AP2)	1 year
	Digital twin prototype calibration	1.5 years
	Digital twin prototype validation in collaboration with AP2	2 years
	Complete initial *in silico* clinical trials	2.5 years
	Establish FDA-compliant digital twin model in collaboration with AP2	3 years
	Complete "pivotal" *in silico* clinical trials with inclusion of TA3 real-world data	4.5 years
TA3	Establish pre-clinical testing platform(s)	9 months
	Complete first set of pilot, pre-clinical modulation studies	1.5 year
	Complete modulation trials on top candidate control points from TA2	3 years
	Demonstrate the possibility of 15%, 25% reduction in ICU stay (directly in pre-clinical model and/or simulation)	3.5, 4.5 years
	Validate TA2/AP2 *in silico* trials on selected targets using pre-clinical and or clinical data	4 years
	Complete platform trial assessment of target modulation (w/AP3)	4.5 years

	Milestone	*Deadline (from Award Date)*
Team Integrator	Complete cross-TA & AP coordination plan	3 months
	Prepare and submit periodic progress reports	monthly
	Conduct end-user and stakeholder engagement activities to guide component and system design and performance.	annually
	Attend annual meeting, participate in "Shark Tank" review with SMEs and stakeholders	annually
	Prepare & update transition (regulatory and commercialization) plan (see section 1.6.5 and Appendix B)	1 year, 2.5 years and semi-annually afterward
	Secure initial commercial partner(s)	2.5 years
	Cross-TA integration: system prototype completion	4 years
	Regulatory submissions for each TA and integrated system(s), with AP collaboration	4.5 years
	Initiate first-in-human adaptive platform trial of integrated CIRCLE system	4.5 years
AP1	Complete initial review of available critical illness data sets and formulate database schema	6 months
	Upload 25%, 100% planned external data, and make available to performers	1, 2 years
	Update database with performer data	1.5y + every 6mo
	Establish query tools (e.g., LLM, GNN)	2.5 years
	Complete database fair access and sustainability plan	3 years
	Integrate TA3/AP3 data from trials	4.5 years
AP2	Complete review of FDA requirements for digital twin compliance and approvals	1 year
	Verify regulatory compliance of digital twin architecture and ML methods	1.25 year
	Provide platform that accepts all performer models for validation studies	1.5 years
	Complete collaborative "pivotal" *in silico* clinical trials of broad ICU population with TA2 groups	4.5 years
AP3	Establish SOPs governing interactions with TA3 performers	1 year
	Finalize plans and SOPs for adaptive platform clinical studies	2 years
	Complete feasibility assessment studies on diagnostic, digital twin and therapeutic modalities in the context of ICU care	2.5 years
	Finalize clinical protocols for clinical studies	3.5 years
	Complete platform trial assessment of target modulation (w/TA3)	4.5 years

*Detailed descriptions are found in Appendix A.

CIRCLE's metrics (Table 2) focus on measuring the progress of technology development in each of the TAs, and the integration of those technologies. In the context of their IV&V role, the AP groups have responsibility for finalizing the metrics evaluation criteria for the TA performers but also have their own metrics for the development of the resources they are to provide to the TA performers and the program. A list of metrics, organized by TA with detailed descriptions can be found in Appendix A.

NOTE: Performers are expected to demonstrate efforts towards meeting <u>all</u> relevant metrics. Unsuccessfully addressing a metric may result in the termination of the award.

*Table 2: Metrics Table**

	Metric name	***Definition***	***Baseline***	***Target***	***Y1***	***Y2***	***Y3***	***Y4***	***Y5***
Each TA	Technological readiness	Modified TRL-scale	TRL-2.5	TRL-6	TRL-3	TRL-3.5	TRL-4	TRL-5	TRL-6
	Usability, Acceptability	% test users satisfied or very satisfied (Likert scale)	0	90			>50%	>75%	≥90%
TA1	Biomarker data collection volume	% of Phase I target submitted to AP1 database	Define quality	Performer specified	>33%	>66%	>100%	≥125%	≥150%
	Frequency	# samples / day (per patient)	2	Min. effective rate for modeling (R)	≥2	≥R	≥2R		
	Multiplexity	# of biomarkers measurable simultaneously	Define quality criteria	Multiplexity (M) needed to support modeling (>50**)	>0.5M	>M	>2M		
	Localization	# of biomarkers accurately measured and attributed to tissue source	Define accuracy	Minimum # (B) needed to support modeling (>10**)		>1	>B	>1.5B	>2B
	Deploy Speed	Time from method deployment to initial data acquisition	SoTA for similar multiplex method (S)	Clinically significant response time (T)	<2S	<(S+T)/2	<T		
	Model Response Time	Time (minutes) required for ingestion of new data and model recalculation state	N/A	10**	60	30	15	10	
	Model biomarker predictive ability	Correct predictions of next biomarker level in time series data (% progress from statistical extrapolation to perfect)	Statistical extrapolation based on prior data	75%**	>20%	>40%	>55%	>75%	≥85%
	Stratification accuracy	Accuracy of separating patients into clinically relevant groups as observed by distinct symptomatic trajectories	Establish methods for definition of trajectory	85%**	>25%	>50%	>75%	>90%	
	Control point identification	# of targets predicted to have beneficial effect if modulated	0	20**		≥2	≥5	≥10	≥20
TA3	Control point (CP) modulation	# of CPs with significant degree of modulation	0	10**		≥1	≥2	≥5	≥10
	Control point (CP) validation	Successful validation (trial) type for at least one CP	Define success	Outcome: lower ICU stay duration		*In silico*	*In silico* / organ / animal	Animal	Human
Team Integrator	Patient state assessment speed (TA1, TA2, AP2)	1/time needed to characterize patient initial state based on biomarkers and digital twin output analysis	Define speed of current practice***	10X faster than baseline			2X	5X	10X
	Patient state assessment breadth (TA1, TA2)	Number of computationally informative variables collected and/or measured, and incorporated into models	Baseline: APACHE III score (20)	10X more complete set of variables (200)	>20	>50	>100	≥200	
	Affordability (TA1, TA2, TA3)	Estimated total cost integrated system.		Cost of comparable acceptable systems (C)			2C	1.5xC	C
AP1	External Data Provision	Upload, formatting and access provision of external critical illness data sets		100%	25%	100%			

AP2	Model testing environment	Provide a software environment for testing, validating and assuring regulatory compliance of TA2-developed digital twin models	Single-model	Head-to-head	Model inte-gration across teams
AP3	ICU-realistic validation infrastructure	Provide access to facilities and resources for usability, acceptability and validation testing in ICU-realistic setting	SOPs	Prototype testing	Valid-ation studies

*Detailed descriptions are found in Appendix A
**Values may be modified at 3-months after program start by agreement among performers, IV&V, subject matter experts and the PM, and will be reviewed periodically
***If it is determined that this is undefined, a different scheme based on a fixed target value may be implemented

1.6.3. Collaboration and Data Sharing

It is expected that all performers will interact and work collaboratively with other performers in developing the methods, technologies, and tools using open, timely, and effective communication, information exchange, and reporting. Performers across all partner organizations will attend common meetings and technical exchanges to advance relevant technologies, bridge across data silos, facilitate transition and commercialization, and move toward transformational care delivery platforms across numerous clinical use cases.

To facilitate the open exchange of information described herein, **performers will have Associate Performer Agreement (APA) language included in their awards.** Each performer will work with other CIRCLE performers to develop APAs that specify the types of information that will be freely shared across performer teams. The open exchange of scientific information will be critical in advancing the software research required to achieve the CIRCLE objectives. The APA will establish a common understanding of expectations to guide the open exchange of ideas and establish a collaborative foundation for the CIRCLE program. All APAs must be completed and in effect within the first 3 months of program performance. Each performer will work with other performers as described above, and specifically:

- Cross-TA team interactions: CIRCLE is focused on making clinically meaningful changes in critical care, and that is likely to emerge from an exchange of ideas from different perspectives. To this end, TA teams will present their progress at semiannual (virtual) and annual (in-person) CIRCLE meetings where they will receive feedback from the other TA teams and ARPA-H designated subject-matter experts (SMEs) and discuss best practices and emerging trends in critical illness, immunology/inflammation biology, and computational modeling. Emphasis will be placed on potential synergies across TA teams regarding novel diagnostics or components thereof, digital twin capabilities, and emerging therapeutic possibilities.
- TA team – AP interactions: ARPA-H is committed to maximizing the impact of each TA team. Accordingly, each TA team will work with AP1 to define their respective data needs and TA1 data-generating capabilities, with AP2 to define the use of TA2 models to support regulatory filings, and with AP3 to define how TA team products will reach the ICU. AP teams will require collaboration and data/code sharing with each TA performer team to carry out their IV&V functions (see section 1.6.4, below). Data sharing requirements between TA and AP performers are detailed in Table 3, below. Specific AP

team evaluations of TA team progress will be shared solely with the corresponding team, but aggregate lessons learned, and suggestions will be discussed across all program performers.

- TA team – transition/commercialization partner interactions: Transition and commercialization are key goals of the CIRCLE program. Thus, TA teams will work with transition and commercialization partners identified by each team and/or identified by ARPA-H toward this goal. In addition to regular updates on commercialization plans in the context of the monthly progress meetings, performers are expected to present details of their commercialization progress confidentially to ARPA-H-appointed panels of SMEs at least annually (and potentially semi-annually), which will generate feedback from the Program Manager to each team.

Table 3: CIRCLE TA performer-AP data sharing requirements

	TA1	TA2	TA3
AP1	• TA1 performers will share deidentified data with the AP1 performer for input into the CIRCLE database	• AP1 performers will enable TA2 performers to access (download) data from the CIRCLE database from all performers (and external sources) for the purpose of training and validating models only. Performers will not use the data from other performers for any other purpose while those data are not available to the public. Such other performer data must be deleted by the downloading performer after this authorized use is completed.	• TA3 performers will collect data on the effects of control point modulation and will, in the same manner as TA1 performers, submit their data to the AP1-administered database
AP2	N/A	• TA2 performers will provide trained models, and all requested information relevant to the models to the AP2 performer for testing and validation • The AP2 performer will provide the results of all testing and validation, including that for head-to-head, and merged-model evaluations to the TA2 performers that created the submitted models	• TA3 performers will provide results from all modulation studies directly to the AP2 performer if requested for the purposes of model validation
AP3	• TA1 performers will provide to the AP3 performer prototypes of diagnostic devices, and related information and data for the purposes of evaluating safety, usability, acceptability and progress towards commercial	• TA2 performers will provide to the AP3 performer prototypes of diagnostic algorithms, data I/O hardware, models and associated software for clinical decision support, and related information and data for the purposes of evaluating safety, usability, acceptability and progress towards	• TA3 performers will provide to the AP3 performer data on all control point modulation experimental methods and outcomes for the purposes of evaluating safety, usability, acceptability and progress towards

	transition, in an ICU-like context • The AP3 performer will provide the results of all evaluations to the TA performers	commercial transition, in an ICU-like context • The AP3 performer will provide the results of all evaluations to the TA performers	commercial transition, in an ICU-like context

1.6.4. Acceleration Platforms (APs) / Independent Verification and Validation (IV&V)

(NOTE: This section describes what tasks the APs will perform and what TA proposers should expect from the AP/IV&V component of the CIRCLE program. Expectations for IV&V performers' proposals can be found in section 1.7.2)

IV&V for the CIRCLE program will be carried out by three AP teams that will be distinct from the TA teams. Each AP team will work with all the TA teams at the level of individual TA components, providing resources to accelerate progress towards milestones, and evaluating progress towards metrics to be reported back to the ARPA-H Program Manager. During the first 3 months of the program, each AP team will collaborate with the TA performers and CIRCLE staff to establish targets and baselines, and finalize metrics, for all the program milestones (see section 1.6). All AP teams will collaborate with the ARPA-H Program Manager in the assembly of panels of experts in the relevant TAs, clinical practice, regulatory process, and commercial transition, for periodic review of TA performer team progress.

TA performers are ***required*** to collaborate with these AP performers throughout the program's duration by providing necessary data, code, and other requested materials for technical evaluations of progress towards all metrics and milestones. AP performers are ***required*** to safeguard proprietary information shared with them and enforce agreed upon data access policies. Validation responsibilities include testing performer-developed methods and code with independently collected data to ensure the generalization of the reported methods to new data and new clinical sites, as well as the verification and validation of simulation tools developed by the performers. The AP performers will be tasked with providing reports to the ARPA-H Program Manager on analysis results; copies of these reports will be provided to the TA performer team involved.

In addition to their validation and verification role, each AP team will provide critical resources and services to support and accelerate the progress of the TA performers.

AP1 (Critical Illness Clinical Data & Analysis Platform) will:

- Interact primarily with TA performers' TA1 components, and support and collaborate with all TA components to promote their research goals.
- Provide guidance to, and assure compliance of, TA1 performers regarding all data sharing, data standardization and data access requirements (see section 1.7.3).
- Collaborate with both TA1 and TA2 components to assure that data contained within and delivered from the database is suitable for performer's use cases.

- Compile critical illness-relevant datasets from external and performer sources (from TA1, TA2 and TA3) into a program database and provide access to all program performers.
- Provide data products (summaries, metrics, views, query tools, and analytical tools potentially including foundation/large language models (LLMs) or related technologies) for performer use to enhance their research productivity.
- Establish data security for the CIRCLE database following applicable regulations and best practices and govern enforcement of data rights and data access control policies.
- Interact with AP2 to define concordance between digital twin *in silico* simulations and ground truth critical illness data.
- Perform analytical tasks based on the CIRCLE database and query tools to establish, for instance, common features of inflammation across critical illness patient subtypes, common proxies for outcome improvements, and common definitions of patient immune state in the context of generalized ICU populations.
- Support TA1 performers in preparation and submission of FDA regulatory documents for diagnostic systems.
- Interact with AP3 to collate data stemming from adaptive clinical trials and make them available to all program performers.

AP2 (FDA-compliant Digital Twin Platform) will:

- Interact primarily with TA performers' TA2 components, and support and collaborate with all TA components to promote their research goals.
- Provide guidance to – and assure compliance of – TA2 performers regarding all model, code and software standardization, sharing and access requirements.
- Provide a digital twin model "sandbox" testing environment (platform) for performance validation and checking for compliance with relevant regulations (for instance from the FDA) and providing advice and assistance to TA performers in achieving compliance. Performers will have access to this system for their own testing and evaluation processes.
- Develop protocols and metrics for evaluating and comparing the *in silico* clinical trials results from and among the TA2 teams.
- Collaborate with the TA2 teams to carry out "pivotal" *in silico* clinical trials of broad ICU populations.
- Support TA performers in the preparation and submission of FDA regulatory documents for digital twins.
- Investigate the possibilities of creating "meta" twins by integrating digital twin models from multiple CIRCLE performers, potentially achieving improved performance.

AP3 (Critical Illness Clinical Trials Platform) will:

- Interact primarily with TA performers' TA3 components to test potential therapies but will also interact with TA1 and TA2 to test potential diagnostic modalities, and support and collaborate with all TA components to promote their research goals.
- Provide planning, guidance and access to resources and facilities to enable and accelerate validation studies carried out by TA3 components, and to test diagnostic modalities developed by TA1 and TA2.
- Evaluate validation studies independently with respect to experimental design, safety, and the assessment of results.
- Provide access to clinical ICU environments and appropriate stakeholders for the testing of all performer technologies for safety, usability, acceptability, etc. in the clinical setting.
- Support TA performers in the preparation and submission of FDA regulatory documents for diagnostic systems and devices, and SaMD and clinical decision support applications.
- Assess the clinical feasibility of integrating performer teams' diagnostic, digital twin and/or therapeutic modalities into existing ICU workflows.
- Establish plans for and facilitate performer participation in platform clinical studies for diagnostic, digital twin and/or therapeutic modalities.
- Collaborate with TA performers in the establishment of clinical protocols for these studies.
- Collaborate in interpreting the results in these studies and their implications for future FDA approvals and transition.

1.6.5. Commercial Transition

Throughout the program, performers are expected to work towards the goal of transitioning their technological advances into the marketplace for the purpose of delivering improved critical care to the American public. To this end, performers will work closely with government, private sector, and hospital partners to refine the commercialization approach for individual and integrated components of CIRCLE technologies. To ensure the long-term sustainability and proliferation of these technologies, performers will develop their respective technologies in a manner that creates incentives for ongoing investment, development, and adoption.

TA proposers must include a commercialization strategy narrative that demonstrates that the proposer team has considered the commercial path of their work, and that they bring the necessary expertise and partnerships to do so. The narrative should include a vision of the anticipated commercialization products, integrations, options for transition including off-ramps for any sub-technologies that may be developed, end-users and markets, business models, Intellectual Property (IP) requirements, and regulatory considerations. Critically, they must also demonstrate a commercialization approach that integrates and leverages the robust validation efforts of the AP teams (section 1.6.4). The commercialization strategy narrative must be included within the Technical & Management Document component of Volume 1 of the proposal (see section 4.3.1) and be no longer than two pages. Appendix B of this ISO includes additional information and an example commercialization roadmap that may be helpful in scoping this section. Proposers are encouraged to have

discussions with potential commercialization partners early and are welcome to include letters of support from such in Volume 1.

Selected teams will be expected to complete a commercialization roadmap within 3 months of the award effective date. This roadmap is expected to be updated periodically based on program progress, including at least at the end of year 3, year 4, and year 5. The Team Integrator lead for each performer team (typically the PL, as noted previously) is expected to hold primary responsibility for the commercialization strategy and roadmap. This roadmap will be developed into a draft commercialization plan including recommendations for ARPA-H commercialization support to be delivered at the end of year 1. Feedback on commercialization strategy will be provided to performers in a timely and appropriate fashion.

Teams may receive support from ARPA-H's dedicated resources. ARPA-H deploys a suite of capabilities for the agency, program managers, and performers that address real-world challenges that make technology transition a hard problem beyond simply scientific discovery. PMs work in close coordination with these resources to ensure commercialization is core consideration of all agency-funded work, at every point in the process—from concept design to graduation.

As indicated in the Milestones section (1.6.2), TA performers are expected to secure initial commercialization partnerships no later than 2.5 years into the period of performance. It is expected that these partners will contribute funding to support commercialization-related activities, particularly in year 4 and year 5 of the Program.

1.7. PROPOSAL FEATURES

Unless otherwise indicated, the term "proposals" refers equally to both Type A (TA) and Type B (AP / IV&V) proposals (see section 1.6.1).

1.7.1. Proposal General Objective

- As indicated in section 1.6.5 above, all Type A (TA) proposals must include within their Technical & Management Document (see section 4.3.1) a Commercialization Strategy Narrative of no more than 2 pages in length.
- All Type A (TA) proposals must include a management plan, as part of the Technical & Management Document (see section 4.3.1), that describes how the team will be managed and how the various sub-team contributions will be designed with interoperability in mind to enable eventual integration of systems, devices, models and software. Proposals should provide a detailed plan for coordination, including explicit plans for interaction among collaborators/subperformers of the proposed effort. As noted above, the Team Integrator component is expected to be a centerpiece of the Technical & Management Document.
- All Type B (AP / IV&V) proposals must include a management plan as part of the Technical & Management Document (see section 4.3.1) that describes how the team will be managed, and how the various sub-team contributions will be designed to assure delivery of both TA performer support through resource provision and

collaboration, and fair and unbiased TA performer evaluation and validation resulting in reporting to the program PM team.

- IP rights asserted by any performer for technologies created under this program must be aligned with IP requirements described in section 1.7.6. Commercially available tools may be leveraged for and/or incorporated into proposed solutions. Licensing details (costs, restrictions, etc.) must align with the overall goals of the program and must not inhibit collaboration among performers, hospital partners, and/or the Government.
- All proposals will include a detailed budget for all phases, and details of key personnel's expertise that align with their stated responsibilities and role(s).
- All proposals will include supplementary individualized milestones (and associated metrics if useful) to enhance the ability of the CIRCLE team to monitor progress towards their goals.
- Proposers are encouraged to organize their technical volume to include three TA sections and an Integrator section. Each TA section should be subdivided into 3 sub-areas (objectives): Preparation, Research, and Development.

1.7.2. TA and AP Specific Objectives

TA1 (Dynamic Immune Descriptor) proposal sections will:

- describe the specific patient population from which data will be obtained and justify why this population will yield data suitable for digital twin modeling and application to the broadest possible population of critically ill patients;
- detail how the proposed methods will provide data that are sufficiently accurate, abundant, frequently sampled, and potentially spatially assigned and/or attributable to source tissues to enable the proposed digital twin models to be successful;
- describe how the proposed sampling methods and frequency are consistent with use in ICU environment, and compatible with integration with exiting ICU equipment and technologies;
- detail how pre-clinical and clinical data will be obtained, including plans for Institutional Animal Care Use Committee (IACUC), IRB and other necessary approvals;
- delineate assessments for defining the acceptability of the proposed technologies with stakeholders such as clinicians, health care systems, insurers and regulators; and
- present a compelling pathway for commercialization of the proposed technology and its integration into the existing ICU environment and workflows.

The following are out of scope for TA1: The application of technologies whose reproducibility, accuracy, precision, and/or reliability are unlikely to be defined sufficiently during Phase I of funding, that are unlikely to be acceptable by hospitals and health systems due to high cost, that require significantly time-consuming off-site processing or analyses, and/or that are specific to only a limited subset of critically ill patients (for instance, analyses related solely to infectious agents and applicable only to those with sepsis).

TA2 (Digital Twin Generator) proposal sections will:

- demonstrate extensive expertise in carrying out mechanistic multiscale computational modeling and generating digital twins, along with the overall architecture, training methods, and analytical tools that will contribute to successful digital twin models of immune processes in critically ill patients;
- describe how data from TA1 and TA3 studies as well as patient data from electronic health records (EHRs) and routine in-ICU data streams will be utilized in constructing, training and using the proposed digital twin models;
- describe the frequency of measurement / updating required for predicting patient trajectories, identifying potential therapeutic control points, and carrying out virtual clinical trials to define recommended use cases for treatments including relevant patient stratifications, intervention timings, and degrees of control point inhibition or stimulation; and
- describe the strategy for operationalizing model personalization to specific patients in ICU-care scenarios for cost-effective and clinically appropriate therapy and treatment.

The following are out of scope for TA2: Methods that do not incorporate individual patient data covering their current trajectory in the ICU, methods that do not connect digital twin model variables to key EHR data variables, approaches that are intrinsically limited to particular patient stratifications or classes within the broader critical illness patient population, and approaches that only classify (stratify) patients, and/or predict patient trajectories without identifying potential therapeutic control points mechanistically.

TA3 (Rational Immune Reprogrammer) proposal sections will:

- address clearly how access to methods, materials (drugs, drug libraries, devices, cells, artificial tissues or organoids, animals, patients), and facilities will be secured to enable validation studies of the widest possible range of control points that may result from TA2 modeling;
- detail how validation methods will maximize the collection of data useful for re-calibrating and improving the TA2 digital twin models; and
- detail plans to engage transition stakeholders (investors, regulators) in the early development of validation strategies that are most likely to lead to adoption and approval of new therapies.

Out of scope for TA3 are proposals involving research into therapeutic modalities that require extensive development during the program timeframe (e.g., starting at TRL 1-2 at the commencement of funding).

AP1 (Critical Illness Clinical Data & Analysis Platform) proposals will:

- demonstrate a track record of work on consolidating, aggregating, and assessing heterogenous datasets involving both clinical and biological data and interacting with multi-institutional research teams in supporting, building, and otherwise enabling such communities;

- detail clear plans for obtaining and aggregating datasets on clinical and biological data related to broad populations of critically ill patients;
- define clearly how human data from TA teams will be checked for quality and aggregated with existing clinical datasets of critical illness;
- detail the process by which relevant data sources will be identified based on TA performers' modeling needs;
- describe the types of data analysis and data access tools (such as LLMs or graph neural network (GNN)-based query systems) that will be incorporated into the CIRCLE database user interface to allow ARPA-H and TA performers to extract relevant data for their modeling efforts;
- detail methods for aggregating synthetic data generated from TA2 digital twin models with datasets on clinical and biological data related to broad populations of critically ill patients and generating large-scale data-driven models therefrom;
- demonstrate experience working with government sources of data and gaining access to those datasets;
- outline sustainability plans for the CIRCLE database and associated systems to extend their availability past the end of the CIRCLE program, and to widen its availability to researchers, clinicians and health care organizations to the benefit of patients (it is not expected that AP1 will participate directly in commercialization activities); and
- have considered and budgeted for the potential costs of obtaining access to private datasets relevant to CIRCLE performers' needs.

The following are out of scope for AP1 proposals: Proposals focused solely on storing or repackaging existing datasets without a demonstrated capacity to aggregate across distinct types of data will be considered out of scope.

AP2 (FDA-compliant Digital Twin Platform) proposals will:

- demonstrate extensive expertise in aggregating and evaluating mechanistic multiscale computational modeling and digital twins;
- establish their capabilities towards providing a computational model (digital twin) testing environment for CIRCLE performer use and the evaluation and validation of their models versus independent data sets, and to demonstrate compliance with FDA regulations;
- establish their expertise in carrying out *in silico* digital clinical trials;
- Define clearly how to compare multiple distinct mechanistic models with regard to frequency of measurement / updating required to define immune system controls points and for relative predictive performance at the individual and population levels; and
- establish the team's expertise with respect to FDA and other regulations regarding digital twins and *in silico* clinical trials in support of specific therapies, as well as the processes of making FDA regulatory document filings.

The following are out of scope for AP2 proposals: Systems supporting only ML or other forms of data-driven modeling (e.g., LLMs), and not mechanistic models and digital twins are out of scope.

AP3 (Critical Illness Clinical Trials Platform) proposals will:

- detail the methods and ICU-like environments they will utilize to evaluate technology prototypes developed by the TA performers;
- describe the stakeholder groups they will access as testers to guarantee robust feedback to the performers, allowing them to iterate in the areas of safety, usability, integration into existing ICU workflows and acceptability;
- detail their experience in providing access to patients, particularly patients suffering from critical illness from diverse causes, for adaptive clinical trials to be used in carrying out TA2/TA3 modulation/validation studies;
- establish plans for facilitating performer participation in platform clinical studies for diagnostic, digital twin and/or therapeutic modalities, establishing clinical protocols for these studies, and collaborating in interpreting the results of these studies and their implications for future FDA approvals and transition; and
- establish the team's expertise with respect to FDA and other regulations regarding diagnostic devices and systems, SaMD, and clinical decision support software, as well as the processes of making FDA regulatory document filings.

The following are out of scope for AP3 proposals: clinical studies focused solely on one sub-population of critically ill patients will be out of scope.

1.7.3. Data Collection and Sharing Requirements

CIRCLE performer teams must manage all data collection and storage activities in accordance with patient privacy rules and best practices. Proposers must include a plan on how their data sharing activities align with the FAIR (Findability, Accessibility, Interoperability and Reuse, www.go-fair.org/fair-principles) principles, data standards, and the data sharing dimensions described below.

Deidentification: All performers must deidentify all personally identifiable information (PII) and protected health information (PHI) in accordance with the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule (45 CFR 164.514) prior to any data sharing, aggregation, or external analysis. Deidentification must include removal of direct and indirect identifiers and be validated using appropriate statistical or expert methods, such as those referenced in NIST SP 800-188. Data not meeting these requirements may not leave the originating institution's protected environment, to include both the originated institution's data infrastructure and any data infrastructure managed by their vendors. Any data set to be shared externally or aggregated across sites must be accompanied by an attestation of de-identification, and the process must be documented and made available to ARPA-H upon request. All procedures and tools used for de-identification are subject to review and approval by ARPA-H or its designee.

Cybersecurity: Performers must be compliant with relevant cybersecurity and privacy

standards. Proposals must identify relevant policies and present adequately detailed plans as to how they will comply with these policies as well as identify and manage vulnerabilities if requested. General (non-health related) safety and cybersecurity standards must be addressed as well.

Public Access: Data that, per performers' attestation and following agreement by the Program Manager are needed directly for commercialization, may be protected by IP rights negotiated with ARPA-H (see section 1.7.6). All other (deidentified) data must be deposited in publicly available repositories[33] within 2 years of data generation, or by the end of the program period of performance, whichever comes first.

Validation and Within-Program Sharing: Data that are generated (collected) under the program (both measured biological data, and synthetic data generated from digital twin models) must be provided to AP1 for both validation and incorporation into CIRCLE data products (see AP1) and for **use** by all other performers to train their digital twin models. Data that are utilized from other sources by performers for the training of their digital twins must be provided to AP1 for validation but may be excluded from incorporation into CIRCLE data products if such exclusion is deemed a necessary condition for its use, per performers' attestation and following agreement by the Program Manager. *NOTE: CIRCLE policies around data sharing among CIRCLE performers are discussed in section 1.6.3, above.*

1.7.4. Data Standardization Requirements:

All data generated by CIRCLE performers, particularly that derived from any new devices and technology created in the CIRCLE program, must be adherent to existing, relevant standards established or endorsed by the Office of the National Coordinator for Health Information Technology (ONC), e.g., HL7, FHIR, DICOM, LOINC, SNOMED CT, USCDI, and USCDI+, or similar, unless performers attest otherwise and following agreement by the Program Manager. Performers are encouraged to leverage mechanistic modeling conventions such as the use of Systems Biology Markup Language (SBML) to facilitate model evaluation by AP2. It is expected that all performers will work together to converge on standards to ensure interoperability across prototype capabilities. Whenever an existing standard is available that meets technical needs of the program, performers must use the existing standard instead of creating their own. In cases where an existing standard provides only partial functionality, performers should extend the existing standard in a fully backwards compatible manner and create the documentation needed for ONC to evaluate extensions for inclusion in the national standard. All work to extend existing standards should be carried out in collaboration with other CIRCLE performers including the appropriate AP performer.

It is expected that data collected might not have standardized data collection formats. Proposers must provide a comprehensive description of any novel data standards they intend to develop and implement. This description should include the rationale behind the proposed standard, detailing how they will address current gaps in data interoperability, accessibility, and security. Additionally, proposers are expected to outline the methodologies and outreach to be employed in creating the standard, and how their adoption will facilitate improved data integration and enhance data quality. Benchmarks for assessing the effectiveness and scalability of the new standards are encouraged to ensure measurable impact and sustainability.

The AP1 performer has the primary responsibility for defining overall CIRCLE data standards and assuring that data incorporated into and accessible from the CIRCLE database meets appropriate data standards for healthcare and clinical and biomedical research. Furthermore, in assuring that TA1 data are standardized for input into the database, they will ensure that those data meet standards for use in ICU settings. AP1 will collaborate with all TA performers at the outset of the performance period and define and communicate all relevant standards by the three-month mark, making updates as needed throughout the program period of performance.

The AP2 performer has the primary responsibility for assuring that digital twins work with standard ontologies and nomenclatures for objects in their models and comply with relevant regulatory standards and best practices[34,35]. AP2 will collaborate with all TA performers at the outset of the performance period and define and communicate all relevant standards by the three-month mark, making updates as needed throughout the program period of performance. These standards should support the development and validation of digital twins, including model and algorithm details/pseudocode, a high-level overview of digital twin development and validation process, standard vocabularies, AI platforms used, cloud sources, and access policies that will determine interoperability and federated data sharing for phenotype data extraction and digital twin deployment across healthcare institutions.

The AP3 performer has the primary responsibility for assuring that clinical data support systems associated with TA2-produced digital twins are compatible and interoperable with relevant in-ICU systems. AP3 will collaborate with all TA performers at the outset of the performance period and define and communicate all relevant standards by the three-month mark, making updates as needed throughout the program period of performance.

1.7.5. Code and Software Requirements

The CIRCLE program will prioritize creating and leveraging open-source technologies and architectures that promote the development of cutting-edge diagnostics and digital twin systems for the benefit of patients. Open-source code is **highly encouraged** using permissive, business-friendly open-source licenses such as CC-BY, BSD, MIT, Apache 2.0 or similar. Performers must describe which deliverables will utilize licenses that ensure public access to the source code, enabling modification, redistribution, and use by both the public and private sectors. *If included*, proposals must detail a plan for the development, documentation, and distribution of the software as open source. Furthermore, the proposal must identify the specific open-source license(s) that will be utilized and provide justification for their selection.

Application Programming Interfaces (API) Requirements

All APIs developed for CIRCLE must be founded on open standards and models such as REST, JSON, JSON-LD and utilize standard data models and ontologies if available, unless performers attest otherwise and obtain agreement from the Program Manager. All data elements and structures in API calls must be mapped to a data dictionary that references the standards.

Performers may not build on top of background intellectual property (IP) – including Limited Rights[36] components (i.e. existing proprietary software) -- unless they have prior written approval from the Program Manager and the Agreements Officer (AO), which would be provided during the negotiations.

Consistent with the IP policies detailed in section 1.7.6 below, if software is to be developed and distributed with commercial or proprietary licenses, this must be asserted in advance (in the appropriate section of the Administrative & National policy Requirements document attachment to this ISO, see section 4.3.1) and is subject to the approval of the Program Manager and ARPA-H's AO based on reasonable negotiations.

Adherence to Government Laws and Policies

Performers will be expected to adhere to all relevant Government laws and policies applicable to data and information systems and technologies, including but not limited to:

- Common IT Security Configurations
- Federal information technology directives and policies
- Section 508 of the Rehabilitation Act of 1973 (29 USC 794d) as amended by P.L. 105-220 under Title IV (Rehabilitation Act Amendments of 1998)
- National Institute of Standards and Technology (NIST) Risk Management Framework Special Publications

1.7.6. Intellectual Property (IP) Requirements

A key goal of the CIRCLE program is to establish a sustainable and interoperable ecosystem for diagnostics, digital twins, and therapeutic control systems that extends beyond the performance period of the program and promotes broad public benefit. Given the diversity of technologies anticipated, proposers must be prepared to assign different levels of rights to the Government depending on the category of IP developed during the program. Proposers must describe how their licensing and rights strategy will support long-term ecosystem sustainability and public access. Time-limited or field-limited exclusivity may be acceptable, subject to ARPA-H approval and program objectives. All assertions of IP rights must be asserted in advance in the appropriate section of the Administrative & National policy Requirements document attachment to this ISO (see section 4.3.1) and are subject to the approval of the Program Manager and ARPA-H's AO based on reasonable negotiations.

Proposals that do not adequately address these requirements — or that seek broad restrictions inconsistent with public benefit goals — may be deemed non-conforming. ARPA-H reserves the right to negotiate IP terms during contract negotiations, based on the technical nature and anticipated utility of each component.

Depending on the TA and technology, ARPA-H will be requiring one of the following IP requirements:

1. Open Access/Public Domain Requirements

All program deliverables that are foundational to interoperability or public reuse — such as annotated datasets, metadata schemas, synthetic data, commons APIs, and validation frameworks — must be delivered with Unlimited Rights[37] and released into the public domain or under open licenses (e.g., CC0, MIT, or similar) unless requested in writing and approved by the Program Manager. These deliverables are considered critical public infrastructure and are expected to support future research and application beyond the CIRCLE program. Timelines for the deposition of data are included in section 1.7.3, above.

2. Government Purpose Rights (GPR) Requirements

All hardware designs and documentation must be provided with a minimum of Government Purpose Rights (GPR),[38] as lesser rights may negatively impact the potential for this health IT ecosystem to become self-sustaining. Software tools, models, algorithms, and integrated systems that are not released under open-source licenses (see section 1.7.5, above), but that contribute directly to shared programmatic functions—such as diagnostic classifiers, control point identification algorithms, or simulation engines — must be delivered with, at a minimum, GPR. This includes all associated source code, documentation, and technical data. Hardware or firmware developed for use in diagnostic or therapeutic monitoring systems must also be provided with GPR.

3. Limited or Negotiated Rights for Commercially Sensitive IP

For certain categories of IP that are expected to form the basis of future commercial offerings—such as novel biomarker panels, repurposed therapeutic regimens, proprietary assays, and personalized treatment protocols — proposers may request flexible licensing treatment.

The proposer must **explicitly request this designation in their proposal** and must **provide a written attestation explaining the commercial potential and rationale for such designation**. Approval will be granted at the discretion of the Program Manager and the Agreements Officer and must be documented in writing.

2. AWARD INFORMATION

This ISO may result in multiple awards of Other Transaction (OT) agreements or no award at all. However, the number of awards selected will depend on the quality of the proposals received and the availability of funds. If warranted, portions of resulting awards may be segregated into pre-priced options. In the event that the Government desires to award only portions of a proposal, negotiations will commence upon selection notification. The Government reserves the right to fund proposals in phases, with options for continued work, as applicable. The Government reserves the right to request any additional 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, cost, and/or the proposer fails to provide requested additional information in a timely manner. The AO shall have sole discretion to negotiate all agreement terms and conditions with selected proposers.

While scientific publications are highly encouraged, ARPA-H will apply publication or other

restrictions, as necessary, if it is determined that the research resulting from the proposed effort will present a high likelihood of disclosing sensitive information including PII, PHI, financial records, proprietary data, and any information marked Sensitive but Unclassified (SBU), Controlled Unclassified Information (CUI), etc. Any award resulting from such a determination will include a requirement for ARPA-H permission before publishing any information or results on the effort.

3. ELIGIBILITY INFORMATION

3.1 ELIGIBLE PROPOSERS

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

3.2 PROHIBITION OF PERFORMER PARTICIPATION FROM FEDERALLY FUNDED RESEARCH AND DEVELOPMENT CENTERS (FFRDCS) AND GOVERNMENT ENTITIES

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

(1) FFRDCs and U.S. Government entities, including federal Government employees, are not permitted to respond to this ISO as a prime or sub-performer on a proposed performer team.

(2) If an FFRDC or U.S. Government entity has a unique research idea that is within the technology scope of this ISO that they would like considered for funding, contact this email address: CIRCLE@arpa-h.gov.

(3) If an FFRDC or U.S. Government entity, including a federal Government employee, is interested in working directly with the Government team supporting the research described by this ISO, the party should contact CIRCLE@arpa-h.gov.

3.3 NON-U.S. ORGANIZATIONS

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. However, non-U.S. entities are encouraged to collaborate with domestic U.S. entities. In no case will awards be made to entities organized under the laws of a covered foreign country (as defined in section 119C of the National Security Act of 1947 (50 U.S.C. § 3059)); a foreign entity of concern meeting any of the criteria in section 10638(3) of the CHIPS and Science Act of 2022; or an individual that is party to a Malign Foreign Talent Recruitment Program (MFTRP), as defined in Section 10638(4) of the CHIPS and Science Act of 2022.

3.4 ORGANIZATIONAL CONFLICTS OF INTEREST (OCI)

Proposers are required to identify and disclose all facts relevant to a potential OCI involving the proposer, its organization, and any proposed team member (proposed sub-performer) (refer to the Administrative & National Policy Attachment). The disclosure must include the proposers', and as applicable, proposed team members' OCI mitigation plans. The OCI mitigation plan(s) must include a description of the actions the proposer has taken, or intends to take, to 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, 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.

3.5 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 within ARPA-H. 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 (proposed sub-performer) providing the support.

3.6 GOVERNMENT CONFLICT OF INTEREST PROCEDURES

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

4. PROPOSAL AND SUBMISSION INFORMATION

ARPA-H will host a Proposers' Day in support of the CIRCLE program. The purpose is to provide potential proposers with information on the program, promote additional discussions, and encourage team networking.

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

4.1 GENERAL GUIDELINES

- Proposers must first submit a solution summary in order to submit a proposal.
- Solution summaries are due no later than the date and time outlined on page 2 of this ISO. Solution summaries received after this time and date will not be reviewed.
- Proposals are due no later than the date and time outlined on page 2 of this ISO. Proposals received after this time and date will not be evaluated.
- All submissions must be written in English with type not smaller than 12-point font. Smaller font may be used for figures, tables, and charts.
- Do not include elaborate brochures or marketing materials; only include information relevant to the submission requirements or evaluation criteria.
- Use of a diagram(s) or figure(s) to depict the essence of the proposed solution is permitted.
- All submissions shall be unclassified.
- Proposers are responsible for clearly identifying proprietary information.
- Submissions containing proprietary information must have the cover page and each page containing such information clearly marked with a label such as "Proprietary" or "Company 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 may publish a Question and Answer (Q&A) document containing responses to all administrative questions submitted regarding this ISO.
- Submissions sent through mediums/channels other than what is prescribed herein, or after the prescribed ISO deadline will not be considered, reviewed, or evaluated.

4.2 SOLUTION SUMMARY RESPONSES

SOLUTION SUMMARY CONTENT AND FORMATTING:

The required solution summary is a mechanism for potential proposers to get feedback prior to proposal submission. All solution summaries submitted in response to this ISO must comply with the content, page, and formatting requirements outlined in Attachment A. Potential proposers are required to use the template provided. Information not explicitly requested in this ISO may not be reviewed.

NOTE: No awards will be made, nor funding provided as a result of solution summary submissions.

SOLUTION SUMMARY SUBMISSIONS:

Solution summaries shall be submitted to the ARPA-H Solution Site at https://solutions.arpa-h.gov/ by the due date and time outlined on page 2 of this ISO. Solution summaries submitted incorrectly (e.g. not submitted to the ARPA-H Solutions Site by the due date and time) will not be considered or reviewed.

ARPA-H will provide written feedback to all solution summary submissions. Feedback at a minimum will provide an encourage or discourage recommendation in submitting a proposal submission. Feedback will be sent to the administrative and technical points of contact noted on the solution summary cover sheet.

4.3 PROPOSAL INSTRUCTIONS

4.3.1 Proposal Volumes

Proposers must provide the following information when submitting a proposal to https://solutions.arpa-h.gov. Template documents and instructions for all volumes are provided along with this ISO. Failure to utilize the templates and/or provide the information requested may result in a proposal being deemed non-conforming and/or delay the review and selection process discussed in Section 5. Proposals should express a consolidated effort in support of either (Type A) all three TAs or (Type B) one of the APs as detailed in section 1.6.1.

VOLUME 1

Volume 1 must consist of the following two documents:

TECHNICAL & MANAGEMENT DOCUMENT (included as Attachment B)

TASK DESCRIPTION DOCUMENT (TDD) (included as Attachment C)

The maximum page count for the Technical & Management document is 40 pages for Type A proposals, or 30 pages for Type B proposals. The Technical & Management document may include an attached bibliography (excluded from the page limit) of relevant technical papers or research notes (published and unpublished) that document the technical ideas and approach upon which the proposal is based. Copies of not more than three relevant papers may be included with the submission and will be excluded from the page limit. Resumes for proposed key personnel must be included in this volume, with a maximum limit of five (5) pages per resume. Resumes will be excluded from the page limit. Letters of support from potential commercialization partners may be included with the submission and will be excluded from the page limit.

Documentation of current Assurance of Compliance with federal regulations for human subjects protection must also be included as an attachment in Volume 1 (per Section 6.3.4) and will be excluded from the page limit. The submission of other supporting materials along with the proposal is strongly discouraged and will not be considered for evaluation.

The TDD must include objectives and associated tasks, aligned with the program milestones. All objectives and tasks must correspond with program phases as described in the Proposal

Structure section (1.6) of the ISO. The TDD does not have a page limit.

VOLUME 2

Volume 2 must consist of the following documents (no page limit):

PRICE/COST PROPOSAL (included as Attachment D)

The Volume 2 Price/Cost proposal must consist of the provided budget spreadsheet and an accompanying budget narrative. The budget narrative must provide enough supporting documentation to justify all elements presented in the budget spreadsheet.

Submissions must include a cost point that is commensurate with the scale and complexity of the proposed technical and management approach. Proposers should ensure that budgets align to the needs of the work being proposed. Budgets should focus on the tasks essential for achieving program goals and associated risk mitigation strategies.

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

VOLUME 3

Volume 3 must consist of the following documents:

MODEL OT AGREEMENT (included as Attachment E)

ADMINISTRATIVE & NATIONAL POLICY REQUIREMENTS (included as Attachment F)

4.3.2 Model Other Transaction (OT) Agreement

Prior to submitting a proposal, proposers must review the Model OT Agreement that is provided as an attachment to this ISO. ARPA-H has provided the Model OT Agreement to expedite the negotiation and award process. The Model OT Agreement is representative of the terms and conditions that ARPA-H intends to include in the resulting award.

Proposers may suggest edits to the Model OT Agreement for consideration by ARPA-H and provide a copy of the Model OT Agreement with track changes as part of the proposal package. It is required that proposers include comments providing rationale for any suggested edits of a non-administrative nature. Suggested edits may be rejected at ARPA-H's discretion, and the AO shall have sole discretion to negotiate any red-lined edits that deviate from the basic terms and conditions. Proposal information should not be included in the Model OT Agreement or in comments on the Model OT Agreement. Any questions, comments, or edits to the Model OT Agreement will not be considered in the evaluation of the proposal.

5. EVALUATION OF SUBMISSIONS

5.1 EVALUATION CRITERIA FOR AWARD

Proposals will be evaluated using the following evaluation criteria, each of which is considered **equally** important.

- **OVERALL SCIENTIFIC AND TECHNICAL MERIT**

  The proposed technical approach is innovative, feasible, achievable, and complete. Task descriptions and associated technical elements provided are complete and in a logical sequence with all proposed deliverables clearly defined such that a final outcome that achieves the goal can be expected as a result of award. The submission identifies major technical risks and planned mitigation efforts are clearly defined and feasible. In addition, the evaluation will take into consideration the extent to which the proposed IP rights structure will potentially impact the Government's ability to transition the technology.

- **PROPOSER'S CAPABILITIES AND/OR RELATED EXPERIENCE**

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

- **PRICE/VALUE ANALYSIS**

  Price and value analysis will be performed on each proposal submission to assess the reasonableness and value of the overall proposed price provided to the Government for the technical solution selected.

  When price and value analysis are inconclusive, cost realism analysis may be performed to ensure proposed costs are realistic for the technical and management approach, reflect the technical goals and objectives of the program accurately, are consistent with the proposer's TDD, and reflect a sufficient understanding of the costs and level of effort needed to successfully accomplish the proposed technical approach. The costs for the prime proposer and proposed sub-proposers should be substantiated by the details provided in the submission (e.g., the type and number of labor hours proposed per task, the types and quantities of materials, equipment and fabrication costs, travel and any other applicable costs and the basis for the estimates). Budgets that are unrealistically high will be viewed unfavorably during the review process.

- **RELEVANCE TO THE ARPA-H MISSION**

  Potential future R&D, commercial, and/or clinical applications of the project proposed, including whether such applications may have the potential to address areas of currently unmet need within biomedicine and improve health outcomes. The degree to which the proposed project has the potential to transform biomedicine is an important factor. The potential for the project to take an interdisciplinary approach is also valuable.

TA Proposals Only: The degree to which commercialization plans are complete, realistic and give confidence that the ARPA-H investment will result in transition to publicly available technology for the benefit of American patients.

5.2 REVIEW AND SELECTION PROCESS

It is the policy of ARPA-H to ensure impartial, equitable, comprehensive proposal evaluations based on the evaluation criteria listed above and to select the source (or sources) whose offer meets the Government's technical, policy, and programmatic goals.

ARPA-H will conduct a scientific and technical review of each conforming proposal. All proposal evaluations will be based solely on the evaluation criteria in Section 5.1.

Relative to the evaluation criteria, the Government will evaluate each conforming proposal, documenting identified strengths and weaknesses. Based on the identified strengths and weaknesses, ARPA-H will determine whether a proposal will be selected for award. Proposals will not be evaluated against each other during the scientific review process but rather evaluated on their own individual merit to determine how well the submission meets the criteria stated in this ISO.

CONFORMING PROPOSALS: Conforming proposals contain all requirements detailed in this ISO. Proposals that fail to include required information may be deemed non-conforming and may be removed from consideration. Non-conforming proposals may be rejected without further review. A proposal will be deemed non-conforming if it fails to meet one or more of the following requirements:

- The proposed concept is applicable to the goals and objectives described in this ISO.
- The proposer meets the eligibility requirements of this ISO.
- The proposal met the submission requirements of this ISO.
- The proposal meets the content and formatting requirements in the attached templates to this ISO.
- The proposal provides sufficient information to assess the validity/feasibility of its claims.
- The proposer has not already received funding or a positive funding decision for the proposed concept (whether from ARPA-H or another Government agency).

NON-CONFORMING PROPOSALS: Proposers will be notified of non-conforming determinations via email correspondence.

An award will be made to the proposer(s) whose proposal is determined to be selectable by the Government, consistent with instructions and evaluation criteria specified herein. Given the limited funding available, not all proposals considered selectable may receive an award and funding.

For the purposes of this evaluation process, a selectable proposal is defined as follows:

SELECTABLE: A selectable proposal is one that has been evaluated by the Government against the evaluation criteria listed in the ISO, and the positive aspects of the overall proposal outweigh its negative aspects. Additionally, there are no accumulated weaknesses that would require extensive negotiations and/or a resubmitted proposal.

For the purposes of this evaluation process, a non-selectable proposal is defined as follows:

NON-SELECTABLE: A proposal is considered non-selectable when the proposal has been evaluated by the Government against the evaluation criteria listed in the ISO, and the positive aspects of the overall proposal do not outweigh its negative aspects. Additionally, there are accumulated weaknesses that would require extensive negotiations and/or a resubmitted proposal.

5.3 HANDLING OF SELECTION SENSITIVE INFORMATION

It is the policy 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, to the extent permitted under applicable laws. Restrictive notices notwithstanding, during the evaluation process, submissions may be handled by ARPA-H support contractors for administrative purposes and/or to assist with technical evaluation.

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

5.4 RESEARCH SECURITY REVIEW (RSR)

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 Requirements 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 MFTRP. It also requires Federal agencies to require recipient institutions 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 conflicts of interest (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 provide research security disclosures as described

in the Administrative & National Policy Requirements 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 a RSR of each proposer and their senior or key personnel after a proposal is selected for negotiations of a potential award. The RSR is not part of the ARPA-H scientific merit review process. 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.

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. AWARDS

6.1 GENERAL GUIDELINES

The AO reserves the right to negotiate directly with the proposer on the terms and conditions prior to award of the resulting OT agreement, including payment terms, and will execute the agreement on behalf of the Government. Proposers are advised that only an AO has the authority to enter into, or modify, a binding agreement on behalf of the United States Government.

6.2 NOTICES

The below-listed notifications will be sent via electronic mail (e-mail) to the Technical and Administrative POCs identified on the proposal coversheet.

6.2.1 Solution Summaries

The following notices will be provided as applicable:

- Notice of discouragement

  The proposer will be informed that their solution summary is discouraged from proposal submission.

- Notice of encouragement

  The proposer will be informed that their solution summary submission is encouraged for proposal submission.

6.2.2 Proposals

The following notices will be provided as applicable:

- Request for clarifying details (if applicable)

  May occur at any time during the evaluation process after proposal submission. Will not include requests for proposal changes and changes will not be permitted.

- Request for additional information (if needed)

  Proposers will be advised of any deficiencies and/or major weaknesses in their proposals and given an opportunity to respond, to include offering proposal amendments.

- Notice of non-selection

  The proposer will be advised their proposal submission has not been selected.

- Notice of selection

  The selection notice will notify the proposer that the Government has selected their proposal for negotiation of a potential award. This notification may indicate that only a part of the effort has been selected for negotiation and may request a revised proposal for only those selected portions, if not apparent through the delineation of proposed tasks.

6.3 ADMINISTRATIVE & NATIONAL POLICY REQUIREMENTS

6.3.1 System for Award Management (SAM) Registration and Universal Identifier Requirements

All proposers must be registered in the System for Award Management (SAM) and must have an active registration, including a Unique Entity ID (UEI) number, at the time of proposal submission. Performers are required to maintain an active SAM.gov registration with up-to-date information throughout the duration of any active Federal award or while their proposal is under consideration by ARPA-H. Registrations in SAM.gov must be eligible for "All Awards." Additional information about SAM.gov registration can be found at SAM.gov.

NOTE: New registrations can take an average of 7-10 business days to process in SAM.gov. Registration requires the following information:

- *SAM UEI number*
- *Taxpayer Identification Number (TIN)*
- *Commercial and Government Entity Code (CAGE) Code. If a proposer does not already have a CAGE code, one will be assigned during SAM registration.*
- *Electronic Funds Transfer information (e.g., proposer's bank account number, routing number, and bank phone or fax number).*

6.3.2 Controlled Unclassified Information (CUI) or Controlled Technical Information (CTI) on Non-DoD Information Systems

Further information on CUI identification, marking, protecting and control is incorporated herein and can be found at 32 CFR 2002.

6.3.3 Intellectual Property (IP)

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.

In addition to a description of IP restrictions within the proposal (detailed in section 1.7), respondents must summarize any IP restrictions in section 6 of the Administrative & National Policy Requirements Document Template. If no restrictions are intended, then the proposal should state "NONE."

6.3.4 Human Subjects Research

All entities submitting a proposal for funding that will involve engagement in human subjects research (as defined in 45 CFR § 46) must provide documentation of one or more current Assurance of Compliance with federal regulations for human subjects protection, including at least a Department of Health and Human Services (HHS), Office of Human Research Protection Federal Wide Assurance. All human subjects research must be reviewed and approved by an IRB, as applicable under 45 CFR § 46 and/or 21 CFR § 50. The human subjects research protocol must include a detailed description of the research plan, study population, risks and benefits of study participation, recruitment and consent process, data collection, and data analysis. Recipients of ARPA-H funding must comply with all applicable laws, regulations, and policies for the ARPA-H funded work. This includes, but is not limited to, laws, regulations, and policies regarding the conduct of human subjects research, such as the U.S. federal regulations protecting human subjects in research (e.g., 45 CFR § 46, 21 CFR § 50, § 56, § 312, § 812) and any other equivalent requirements of the applicable jurisdiction.

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

Funding cannot be used toward human subjects research until ALL approvals are granted.

6.3.5 Animal Subjects Research

Award recipients performing research, experimentation, or testing involving the use of animals shall comply with the laws, regulations, and policies on animal acquisition,

transport, care, handling, and use as outlined in: (i) 9 CFR parts 1-4, U.S. Department of Agriculture rules that implement the Animal Welfare Act of 1966, as amended, (7 U.S.C. § 2131-2159); (ii) the Public Health Service Policy on Humane Care and Use of Laboratory Animals,[1] which incorporates the "U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training,"[2] and "Guide for the Care and Use of Laboratory Animals" (8th Edition).[3]

Proposers must complete and submit the Vertebrate Animal Section worksheet for all proposed research anticipating Animal Subject Research. All Animal Use Research must undergo review and approval by the local IACUC prior to incurring any costs related to the animal use research.

6.4 ELECTRONIC INVOICING AND PAYMENTS

Performers will be required to register and submit invoices directly to the Payment Management System (PMS) unless an exception applies. PMS guidance can be found here: https://pms.psc.gov/training/grant-recipient-training.html.

7. COMMUNICATIONS

ARPA-H intends to use e-mail for all correspondence regarding this ISO. Administrative questions regarding this ISO should be emailed to the CIRCLE ISO Coordinator. ARPA-H may post a Q&A document to SAM.gov regarding all administrative questions submitted to this ISO on an as needed basis. All questions must be in English and must include the name, email address, and telephone number of a POC.

ARPA-H will attempt to answer questions in a timely manner. In order to receive a response sufficiently in advance of the proposal due date, questions should be submitted on or before the Q&A deadline outlined on page 2 of this ISO.

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

Appendix A

Detailed Milestones and Metrics Descriptions

1. Milestones Timeline and details (see Section 2 for Metrics details):

Program Start

(All performer leadership) ***Kickoff meeting****:* Attendance is required (in person) and should include the PL and lead personnel from each of the TAs of the main performer teams and APs. The kickoff meeting will be a 1-day event held as soon as is practical after the initiation of performer contracts, at a location to be determined by the Program Manager.

~Monthly

(Team Integrators and all TA and AP performers) ***Periodic Reporting and Progress Review****:* Detailed cadence and content requirements will be set by the Program Manager in consultation with the IV&V teams. These may include (but are not limited to) written reports, slide presentations, quad charts, data, software or schema deposition, demonstrations (virtual, or at site visits) and/or oral presentations. IV&V teams and SMEs will review monthly reports and provide feedback to the Program Manager and the TA performer teams.

3 months

(All TA and AP performers) ***Metrics Preparation Report****:* IV&V will present details of all metrics baselines, methods, and targets for the program. These details will have been established after collaborative interactions among the IV&V and TA performer groups and approved by the Program Manager. Where appropriate, these parameters may be revised during the program as approved by the Program Manager.

(Team Integrator) ***Coordination Plan****:* Each Team Integrator will provide a document detailing the management and coordination among the performer's TA groups that will lead to achieving the various cross-TA milestones and metrics, particularly those tasks involving integration, regulatory processes, clinical/provider/health system, payor, and commercial transition. The report will also provide a framework for interactions between the Team Integrator and the various TA sub-team leads and POCs, and the corresponding IV&V AP teams, as well as other ARPA-H resources that may be made available to the performers.

6 months

(all TA performers) ***Methods Planning Report****:* All TA performer groups will finalize and submit detailed plans for research methods and activities to take place during Phase I, including obtaining required approvals (for instance, IRBs/IACUCs), or appropriate steps towards obtaining such approvals.

(AP1) ***Database Preparations Report****:* The AP1 team will complete a survey of available datasets relevant to the program to include those held by the US Government as well as public and private sources that may be accessible. In coordination with this effort, AP1 will consult with the various TA performers across all TAs and ascertain the data sources and data types that would be of highest value to them and to the program in general and prioritize sources of those data. Based on these results, AP1 will formulate a database schema and architecture best suited to house, query and deliver those data to the performer teams.

9 months

(TA3) ***Pre-clinical/Clinical Testing Platform(s)****:* TA3 will demonstrate the feasibility of all pre-clinical and/or clinical testing designs, modalities, platforms and methods to be utilized in Phase I of the program.

The purpose of such investigations will be to establish the ability to modulate data- and model-derived control points in patients in a safe and efficacious manner, where efficacy includes measures of sufficient amount of change, speed, specificity, and localization to effectuate a beneficial alteration of patient trajectory in the ICU.

1 year

(Each TA and Team Integrator) ***Meet Year 1 Metrics Targets.*** See below.

(TA1, TA2) ***Biomarker Identification****: TA1 will identify an initial set of biomarkers that can be accurately measured in the ICU context with the necessary frequency and spatial resolution to inform the digital twin models under development by TA2, that enable those models to determine potential control points in stratified ICU patient groups.*

(AP1) ***Meet Initial External Data Upload and Availability Target****:* Based on an assessment of the total number of data sources and/or total data volume planned to be included in the CIRCLE database from non-performer sources, the AP1 team will have ingested and formatted 25% of that target and made it accessible to the performer teams for testing.

(TA2) ***Establish Digital Twin Modeling and Analysis Methods****:* Digital twin model architecture and ML methods to be applied by TA2 teams will be documented to allow the AP2 IV&V team to verify and evaluate these designs and provide collaborative input. TA2 teams will provide sufficient information and data to allow this evaluation to be carried out effectively (see AP2 milestone at 1.25 years, below).

(AP2) ***Complete FDA Requirements Review****:* With an understanding of the types of models under development by the TA2 teams, AP2 will review all relevant FDA requirements for the use of such models in the context of an ICU environment and compile that information for presentation to the performers. AP2 will use this framework to advise and aid the TA2 teams going forward in assuring that their products will be FDA-compliant.

(AP3) ***Standardize Protocols for Collaboration with TA3 Performers****:* AP3 will work with TA3 and the Team Integrators to assess the requirements of each performer team's immune modulation strategy to determine feasibility of deployment to the various centers that will carry out adaptive clinical trials of these modulation strategies. It is anticipated that this process will also involve the initiation of documents necessary for carrying out adaptive clinical trials.

(Team Integrators) ***Prepare Draft Commercial Transition (Commercialization) Plan****:* In collaboration with ARPA-H-provided resources, performers will report initial plans to develop TA-specific and partially or fully integrated systems into commercially viable products that can transition into use in ICU environments for the benefit of patients in a sustainable manner after the end point of the CIRCLE program. Additional details for this and other commercialization milestones can be found in Appendix B.

Annually

(Team Integrators, each TA) ***End-user Community and Stakeholder Engagement:*** To incorporate input from the communities that will utilize the final products of the CIRCLE program, teams will facilitate engagement annually as inputs to the design and refinement process, and in anticipation of the annual progress reviews.

(Team Integrators, APs) ***Annual Meeting & Progress Review****:* In-person all-team annual meetings will be an opportunity for performers to meet with each other collaboratively, present their progress and engage with the ARPA-H team. As part of annual meetings, the ARPA-H and AP teams will provide groups of government and external SMEs, particularly those with clinical and medical products commercialization

and development, to review performer progress via in-person presentations and Q&A sessions. Program year end reporting (and particularly at the end of Phases) will be retrospective of all performance to date.

(TA1) ***Assess Samples****:* TA1 teams will perform assessments (and data collection) from 25% of all planned samples to be used for Digital Twin training each year until all are complete. Additional sample assessments may be carried out in year 5. Samples assessed during TA3 validation studies are separate from this Milestone. This is a separate activity from preparing and cleaning the resultant data for upload to the AP1-managed CIRCLE database.

1.25 years

(TA1) ***Biomarker Assessment Demonstration****:* Following up on the Biomarker Identification milestone at 1 year, TA1 performers will provide data, and potentially a live demonstration in connection with a site visit, of the assessment of identified biomarkers. Teams will demonstrate the tractability of meeting future data collection quality measures and metrics (reproducibility, accuracy, frequency, speed, and spatial resolution) for calibration of and use by the TA2 digital twin models.

(AP2) ***Verify Compliance of Modeling Architecture and Analysis Methods****:* Based on the FDA requirements review, and TA2's report on methods (see 1-year milestones, above), the AP2 IV&V team will verify and evaluate the compliance and FDA compatibility of these designs and provide collaborative input towards achieving that compliance.

1.5 years

(AP1) ***Initial Update of Database with Performer Data****:* AP1 will integrate data generated by performer teams into the larger CIRCLE database. Further uploads will be carried out on an (at least) every 6-months cadence.

(TA2) ***Digital Twin Prototype Calibration****:* TA2 teams will present initial calibration data for their models demonstrating how patient-specific data have been incorporated and parameters identified and adjusted to enable the prediction of biomarker levels and patient trajectories.

(AP2) ***Provide Modeling Validation Platform****:* AP2 will provide a framework, processes, and guidelines for testing and validating performer-generated digital twin models that will support, enhance, and accelerate the process of FDA-compliant digital twin production and overall system integration in the CIRCLE program.

(TA3) ***Complete 1st Set of Pilot Modulation Studies****:* TA3 teams will present the results of their methods to modulate the levels of selected biomarkers in a manner consistent with the control point targets indicated by the TA2 digital twin model outputs.

2 years

(Each TA and Team Integrator) ***Meet Year 2 Metrics Targets.*** See below.

(AP1) ***Complete External Data Upload****:* Based on an initial assessment of the total number of data sources and/or total data volume planned to be included in the CIRCLE database from non-performer sources, the AP1 team will have ingested and formatted 100% of that target and made it accessible to the performer teams. Following this point, additional external data will be added to the database as they become available, and as requested by the performer teams.

(TA2, AP2) ***Digital Twin Prototype Validation****:* TA2-produced and calibrated digital twin models will be tested based on their abilities to produce accurate predictions of future biomarker levels and patient trajectories versus test time-course data available in the CIRCLE database and/or performer data. AP2 will evaluate these validation processes and results and report on the progress of the performer teams.

(AP3) ***Finalize Plans and SOPs for Adaptive Platform Clinical Studies****:* In collaboration with TA3 performers, AP3 will provide streamlined access and procedures for performers to test the modulation of control points using their selected technologies in adaptive platform clinical studies.

(Team Integrators) ***Annual Meeting & Progress Review****:* See year 1 description above.

2.5 years

(AP1) ***Establish Database Query Tools****:* AP1 will develop and deploy user-friendly and powerful tools that will allow performers to access and extract data from the CIRCLE database. Among other modalities, AP1 will investigate LLM, GNN, or similar technologies to allow natural language, AI-informed, or other advanced methods for retrieving and analyzing data.

(TA2) ***Complete* in silico *Clinical Trials****:* Focusing on previously identified control points, TA2 will report on the results of *in silico* trials of simulated modulation conditions (magnitude, timing, duration, etc.) on synthetic populations of patients from various stratifications.

(AP3) ***Complete Feasibility Assessments****:* AP3 will report the results of feasibility assessments on diagnostic, digital twin, therapeutic methods, and planned integrated systems in development by the performers. Feasibility will be judged based (in part) on the compatibility of the methods with use in the ICU environment and the likelihood of meeting effectiveness, cost, usability and acceptability criteria.

(Team Integrators) ***Secure Initial Commercial/Transition Partner****:* Performer teams will demonstrate the commitment of external entities to partner with the prime performer for the purpose of supporting commercial transition in the period immediately following the end of the CIRCLE program's period of performance. Methods of demonstration include letters of commitment, letters of intent, in-kind donations of materiel, provision of advisors, and contribution funds.

(Team Integrators) ***Update Commercial Transition (Commercialization) Plan****:* In collaboration with the CIRCLE Transition Mentor team, and any ARPA-H-provided resources, performers will report final plans to develop TA-specific and partially or fully integrated systems into commercially viable products that can transition into use in ICU environments for the benefit of patients in a sustainable manner after the end point of the CIRCLE program. Additional details for this and other commercialization milestones can be found in Appendix B. Updates to Commercialization Plans are due every 6 months.

3 years

(Each TA and Team Integrator) ***Meet Year 3 Metrics Targets.*** See below.

(AP1) ***Complete Database Fair Access and Sustainability Plan****:* AP1 will develop and submit plans for a viable path to establish the long-term availability of the data and any associated tools or products of the CIRCLE database. Plans should include accessibility of data to all interested parties consistent with the development of improved critical illness care, or other health care benefits.

(TA2) ***Establish FDA-compliant Digital Twin****:* With the assistance of AP2, performers will demonstrate that their digital twin models are FDA-compliant and on track for future approvals by the FDA for use in the ICU environment.

(TA3) ***Complete Modulation Trials on Top Candidate Control Points****:* Complete trials of TA2-provided top control point candidates showing successful modulation and measurement of effects on biomarker levels and (predicted or actual) patient trajectories.

(Team Integrators) ***Annual Meeting & Progress Review****:* See year 1 description above.

3.5 years

(TA3) ***Demonstrate Interim ICU Stay Reduction Target****:* Using estimates, statistical approaches or simulations (in coordination with TA2), and pre-clinical data, provide evidence that the observed control point modulations and subsequent effects would result in at least a 15% reduction in the average ICU length of stay for the targeted patient population. Performers should also demonstrate any alternative predicted clinical outcome improvements that result from their work.

(AP3) ***Finalize Protocols for Clinical Studies****:* In advance of TA3 teams initiating first-in-human clinical studies, AP3 will provide detailed protocols and advice for TA3 teams as they develop the details of their adaptive platform trials.

4 years

(Each TA and Team Integrator) ***Meet Year 4 Metrics Targets.*** See below.

(TA3) ***Validate TA2/AP2* in silico *Clinical Trials on Selected Targets****:* TA2 *in silico* clinical trials completed by year 2.5 will have provided predicted trajectories of patients in response to control point modulations. TA3 will report on data that validates these trials using pre-clinical or clinical data and actual control point modulations.

(Team Integrators) ***Demonstrate (cross-TA) System Prototype Integration****:* Proposer teams will show, through reports, videos, and real-time virtual or in-person demonstrations how components from TAs 1-3 are integrated to create a unified prototype CIRCLE system.

(Team Integrators) ***Finalize Commercial Transition (Commercialization) Plan****:* In collaboration with the CIRCLE Transition Mentor team, and any ARPA-H-provided resources, performers will report final plans to develop TA-specific and partially or fully integrated systems into commercially viable products that can transition into use in ICU environments for the benefit of patients in a sustainable manner after the end point of the CIRCLE program.

(Team Integrators) ***Annual Meeting & Progress Review****:* See year 1 description above.

4.5 years

(AP1) ***Integrate TA3/AP3 Clinical Studies Data into Database****:* The data generated by TA3 teams in their patient-focused studies will be successfully incorporated into the CIRCLE database, and a plan for the inclusion of all data through the end of the program will be presented.

(TA2/AP2) ***Complete "Pivotal" in silico Clinical Trials****:* Incorporating data from prior *in silico* clinical trials, TA3-generated pre-clinical and clinical data (if available), and updated model parameters, TA2 and AP2 will present the results of *in silico* clinical trials that are suitable for regulatory submissions, have high standards of reliability, extensive validation, are comprehensive, and are capable of making clear, decisive recommendations for clinical care of a broad population critically ill patients.

(TA3) ***Demonstrate Final ICU Stay Reduction Target****:* Using estimates, statistical approaches, or simulations (in coordination with TA2), and pre-clinical data, provide evidence that the observed control point modulations and subsequent effects would result in a 25% reduction in the average ICU length of stay for the targeted patient population. Performers should also demonstrate any alternative predicted clinical outcome improvements that result from their work.

(TA3/AP3) ***Complete Platform Trial Assessment of Target Modulation****:* Performers will report on the results (to date) of adaptive platform clinical trials on selected control point target modulation(s), including validation of model predictions, and estimates of benefit to patients.

(Team Integrators) ***Regulatory Submissions****:* Performer teams will make documentary submissions to regulatory bodies appropriate to the level of development for each TA technology product, and each combined partial and complete integrated system instance.

(Team Integrators) ***Initiate First-in-Human Adaptive Platform Trial of Integrated System****:* Performers will initiate clinical studies in collaboration with AP3 for integrated systems that include TA1-developed biomarker assay and diagnostic components, TA2-developed digital twin models, and TA3-developed target modulation techniques in ICU-like settings.

5 years

(Each TA and Team Integrator) ***Meet Year 5 Metrics Targets.*** See below.

(Team Integrators) ***Program-End Meeting & Progress Review****:* See year 1 description above.

2. Metrics detailed descriptions (*NOTE: Annual metrics targets are indicated in the metrics table in section 1.6.2*)

Technological Readiness (all TAs): A modified TRL will be implemented for this metric and are based on definitions established by the Department of HHS for diagnostics, therapeutic devices and drugs or biologicals[39]. Performers are expected to begin the program at a TRL of 2.5, as demonstrated in their proposals. Typically, TRL-2 represents the development of product hypotheses. Here, TRL-2.5 additionally includes the generation of initial preliminary results or data, although not necessarily in context required of the CIRCLE program. TRL-3: experimental proof-of-concept in CIRCLE context, TRL-3.5: generation of testable hypotheses, TRL-4: Lab validation, TRL-5: Component evaluation in ICU-like setting. TRL-6: System-level evaluation in ICU-like setting. Further details of TRLs pertaining to each TA will be developed and disseminated to the teams by the corresponding AP performers.

Usability (Team Integrator, all TAs): Performers will survey a sufficient sample of test users of their technology. Test users must include clinicians familiar with current ICU technology systems and practice. Survey questions with Likert scale responses should probe the satisfaction of the users with the usability of the technology potentially including the concepts of intuitiveness, effort required, training requirements, speed and ease of setup and use, effectiveness, efficiency, and user-error tolerance.

Acceptability (Team Integrator, all TAs): Performers will survey a sufficient sample of test users of their technology. Test users must include clinicians familiar with current ICU technology systems, interventions, clinical decision support systems and practice. Survey questions with Likert scale responses should probe the satisfaction of the users with the acceptability of the technology, potentially including the concepts of the utility and value of the technology outputs, the trust users have in and reliability of those outputs, any ethical concerns with the use of the system or its components, the ease with which the technology can be integrated into existing workflows, the perceptions of the technology that will be encountered when its use is presented to patients and their families, the needs for ongoing training or support to effectively use the technology, the existence of blockers or barriers to adopting the technology, the degree to which the technology improves or degrades the process of making decisions in the ICU, and the degree to which stakeholders views were taken into account in the design and execution of the technology and products, including the views of patients, clinicians, payors and regulators.

Biomarker Data Collection Volume (TA1): Performers will establish a target volume of data (of acceptable quality) to be collected and submitted to the program database by the end of Phase I in coordination with their TA2 sub team sufficient to achieve all TA2 goals and metrics. In coordination with AP1, these data will be evaluated for versus quality criteria to be established within the first 3 months of the program. Only the submission of data that passes the quality check will count towards fulfilling the metrics

targets. Performers are expected to continue collection of data of value to the TA2 modeling and model refinement process throughout Phase II and Phase III of the program as indicated in the metrics targets.

Sampling Frequency Rate (TA1): Performers will establish, in coordination with their TA2 and TA3 sub-teams, as well as the AP2 and AP3 teams, the minimum effective rate of repeated sampling of individual patients required to enable modeling and effective intervention given the typical rate of change of state in critically ill patients. This target rate will be the same for all performers.

Biomarker Detection Multiplexity (TA1): AP1 will establish quality criteria for biomarker measurements. Target multiplexity (M) of biomarker measurement methods will be set based on the minimal requirements for modeling as established by AP2 in consultation with the TA2 teams. Teams are expected to exceed this minimal requirement by at least a factor of 2.

Biomarker Localization Accuracy (TA1): AP1, with the input of TA performers and the other AP teams will define accuracy and target number for the purposes of this metric. Depending on the technologies being developed by the performers, this metric may vary in how it is evaluated. In principle, performers should be able to measure biomarkers in circulation as well as at the source of their production or infer the location of their production from measurements in the circulation. Biomarkers may not show up in circulation in measurable amounts at early enough time points for useful modeling or intervention, thus technologies that can provide localization are of particular importance. The target for the number of biomarkers that can be accurately assigned in this way will be determined considering the modeling needs of the performer.

Sampling Method Deployment Speed (TA1): Reducing the time between initial implementation of sampling methods at the bedside and the initiation of data availability to TA2 models is critical both for effective delivery of time-critical care, but also for minimizing the impact on ICU staff. As a baseline, in consultation with all TA1 performers, AP1 will pick an appropriate comparator benchmark multiplex blood analysis sampling and biomarker measurement system (for instance, white blood cell typing of CD4/CD8 markers at 24-48 hours). Additionally, in consultation with TA2, TA3, AP2 and AP3 performers, AP1 will set a deployment time target representing a value that affords an achievable but significant improvement over the baseline (for instance, comparable to routine blood tests at 1-2 hours).

Model Response/Refresh Time (TA2): The purpose of this metric is to assure that the limitations of model calculation, refresh and output do not present a bottleneck or limitation to the overall system. The initial target values (60 down to 10 minutes) in the metrics table are placeholders and will be finalized by the AP2 team.

Model Biomarker Predictive Ability (TA2): AP2, with inputs from performers, will define the limits of accurate (correct) prediction for future levels of modeled biomarkers, as well as span of time steps for prediction accuracy. Predictions may be made based on external data sets or TA1-generated time series where the models are exposed to data up to a certain time point and then must correctly project future values. The baseline for predictive accuracy will be based on statistical extrapolation of prior data (for instance using curve fitting). It is expected that the variation of biomarker values will be highly non-linear, exhibiting rapid changes in value indicative of changes of state in the patient that cannot be captured simply by extrapolation of prior values.

Model Stratification Accuracy (TA2): AP2 will define parameters for assessing stratification accuracy. Stratification will be based on patient historic (derived from the electronic health record) and in-ICU time series data up to specified points, and subsequent predictions of overall patient trajectory groups. Stratification should be into groups from which distinct control points and interventions may be identified to alter patient trajectories towards healthier states.

Control Point Identification (TA2): Performers' models will identify control points – distinct, feasible targets that can realistically be modulated to beneficially alter patient health trajectories. These control

points should be predicted to be effective on model-driven stratification groupings of patients, and do not necessarily have to be predicted to be effective in isolation of other possible therapeutic interventions. AP2 will define the minimum level of predicted benefit for a target to qualify for counting as a control point.

Control Point Modulation (TA3): Performers will demonstrate the ability to change the levels of model-predicted control points in the direction and magnitude predicted to result in beneficial changes to patient trajectories. These observed changes should be made in the localization context (in the circulation or in target tissues) where they are predicted to be effective.

Control Point Validation (TA3): Performers will collect biomarker data following the successful modulation of control points for comparison with levels predicted by TA2 models. The biomarkers to be tracked will be the set of those modeled in TA2. AP2 and AP3 will develop success criteria for these validation studies. Studies will be carried out in a series of experimental systems of increasing clinical relevance.

Patient Immune State Assessment Speed (TA1, TA2, AP2, Team Integrator): This metric will encompass the time from TA1-developed biomarker assessment methods begin deployment at the patient to the first point at which the TA2 models can make a prediction as to the patient's stratification and future trajectory. AP2, in collaboration with TA performer team input will determine the baseline speed of comparable state of the art assessment methods if any exist. If there are none, a target speed will be set based on the clinical benefit of rapid assessment and early application of immune modulation that is reasonably achievable.

Patient State Assessment Breadth (TA1, TA2, Team Integrator): TA2 models will improve upon the current state of the art in assessing ICU patient state by incorporating computationally informative variables from patient health records, generally available ICU monitors and tests, and TA1-biomarker platforms. The baseline of 20 input variables is based on the current APACHE III score system[40]. The target is a 10x increase in variable breadth to at least 200 input variables.

Component and System Affordability (Team Integrator): Performers will assess the overall cost to an average health care system of utilizing the complete CIRCLE measure/model/modulate instance they will deploy. Performers will also estimate the average benefit to patients in terms of reduced time spent in the ICU. The metric will be the average cost of an ICU stay considering both the added costs of the system and the reduced length of stay. The target will be a cost comparable to other systems found acceptable by major hospital ICU systems.

External Data Provision (AP1): The AP1 IV&V performer will create a program database to house both external and performer-generated datasets. Within the first 3 months, in consultation with performers, and having reviewed the data availability landscape, the performer will establish a set of external data sets to include in the database for performer use. This data will be included and made available based on the targets indicated in the metrics table (Section 1.6.2).

Model Testing Environment (AP2): The AP2 IV&V performer will provide a software environment for testing, validating and assuring regulatory compliance of TA2-developed digital twin models. According to the target schedule in the metrics table (Section 1.6.2), the environment will include the capabilities to evaluate individual models, to evaluate models in head-to-head comparison, and to combine models into integrated systems (meta-models), and evaluate their performance.

ICU-realistic Validation Infrastructure (AP3): The AP3 IV&V performer will provide access to facilities and resources for usability, acceptability and validation testing in ICU-realistic settings. According to the target schedule in the metrics table (Section 1.6.2), the performer will provide SOPs for performing evaluations, provide testing of prototypes from each of the program TA sub-teams, and perform validation studies on

those systems and any integrated systems that are produced.

Appendix B

ARPA-H Commercialization Roadmap

Working with ARPA-H

Following Program Kickoff, ARPA-H will review the awarded performers' commercialization strategy narrative and provide feedback on key areas like market landscape, regulatory, IP, investor and stakeholder outreach. Feedback might include direct engagement with ARPA-H capabilities, as coordinated by the Program Manager.

As indicated in the CIRCLE milestones table (section 1.6.2), performers shall turn their initial commercialization strategy into a draft plan at 2.5 years after Award. This plan shall establish commercialization milestones that are assessed and updated regularly to optimize the likelihood for successful commercialization of the proposed technology. This plan will be updated every 6 months through the period of performance.

Preparing a Draft Commercialization Plan

ARPA-H will provide a template for the commercialization plan, and awarded performers will be responsible for submitting a draft commercialization plan at the end of program year 1. Depending on the performer and technology readiness level (TRL), the draft commercialization plan could include customer discovery, market analysis, financial projections, technology transfer plan (licensing, spinout, etc.), management and operational plan, IP, clinical and regulatory strategy, sales and marketing strategy. The draft plan should include related commercial activities and timeline as well as setting the commercialization milestones for the current and future phases of the program. It is expected that the commercialization plan will evolve over time as technical and commercialization milestones are met. ARPA-H will work with the performer and PM team to update the commercialization plan and identify ARPA-H commercialization capabilities available to performers so that they can meet and accelerate their commercialization milestones. A full commercialization plan should be submitted by end of second quarter of program year 2, unless otherwise approved by ARPA-H. Performers must provide an updated plan bi-annually until the end of the period of program performance.

CIRCLE Commercialization Roadmap

The commercialization roadmap below has been created as a guide to address commercialization-related activities. These activities may not be relevant or appropriate for all proposers. Proposers may suggest adjusted or alternate activities that align to their technical approach and relevant transition and commercialization strategy.

Commercialization Roadmap

Integrated Platform	
FY26	Phase I.I
End User/Market	• Defined target users and care pathway • Analysis of customer interviews to identify and understand initial challenges and opportunities
Business Model	• Market analysis and competitor analysis results • Reimbursement strategy

IP	• Identify and categorize IP assets. Complete IP risk assessment and patent filing timeline. Begin process to secure legal protection along with IP strategy and management planning
Regulatory	• Regulatory roadmap to include intended use(s), treatment modality, classification, and risk management assessment
Exit Plan	• Investor strategy • Interview results with 10 ICU clinicians and care pathway personnel for concept and early adoption interest
FY27	Phase I.II
End User/Market	• Initial go-to-market strategy • Comprehensive stakeholder engagement plan across product scenarios that includes all key user groups from clinicians to hospital IT departments • Clickable prototype
Business Model	• Portfolio of business models for each type of market segments (academic medical center, community hospitals, value-based care vs. fee-for-service, etc.) to include all assets
IP	• Finalize IP strategy and management including conducting a freedom-to-operate (FTO) analysis and file IP on any identified patient portfolio gaps plans • Provide plans for commercialization and licensing, along with a licensing agreement template.
Regulatory	• Regulatory – system architecture design specifications and therapeutic device documentation. Additional documents in pre-sub package. • Pre-submission meeting summary results
Exit Plan	• Results of strategic investor engagement • Value proposition demonstrates pathway to improvement of critical care outcomes and economics
FY28	Phase I.III
End User/Market	• User feedback results on clickable prototype
Business Model	• Pricing strategy for each commercial product(s) • Reimbursement coding strategy
Regulatory	• Summary of pre-clinical test results, clinical validation report and software and hardware validation report
Exit Plan	• Ownership summary of all anticipated assets • Information on initial commercial partner(s) obtained
FY29	Phase II
End User/Market	• Market access strategy • Proposed marketing claims to match clinical endpoints • User training feedback provided from 3 hospital providers, at least 10 stakeholders
Business Model	• Financial forecasts for early revenue scenarios • Results of interviews from 3 payors • Real-world evidence collection plan

Regulatory	• FDA submission package, summary of regulatory consultant and FDA communications • Post-market surveillance plan
Final	Final Commercialization Plan Phase III
Product Development	• All previous annual commercialization plans included • Clinical development plan
Business Model	• Health Economics and Outcomes Research (HEOR) data analysis results • Payor pilot established with 1 hospital for evidence generation
IP	• IP summary including all IP ownership and licensing terms outlined
Regulatory	• FDA submission and communication updates
Exit Plan	• Investor summary with at least 1 strategic partnership and/or acquisition interest for transition outlined • Exit plan summary of all assets to be transitioned

Commercialization Timeline

Commercialization Roadmap	Included in this ISO
Commercialization Strategy Narrative	Proposers submit in proposals
Draft Commercialization Plan & Milestones	End of Program Year 1
Full Commercialization Plan	Program Year 2, end of Q2 and updated biannually

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