AMENDMENT OF SOLICITATION/MODIFICATION OF CONTRACT

1. CONTRACT D CODE	PAGE OF PAGES
	1 2

2. AMENDMENT/MODIFICATION NO.	3. EFFECTIVE DATE	4. REQUISITION/PURCHASE REQ. NO.	5. PROJECT NO. *(If applicable)*
P00001	See Block 16C	OS257065	

6. ISSUED BY	CODE	7. ADMINISTERED BY *(If other than Item 6)*	CODE
ASPR-BARDA	ASPR-BARDA	ASPR-BARDA	ASPR-BARDA

ASPR-BARDA
200 Independence Ave., S.W.
Room 640-G
Washington DC 20201

ASPR-BARDA
US DEPT OF HEALTH & HUMAN SERVICES
BIOMEDICAL ADVANCED RESEACH & DEVELOPMENT AUT
200 INDEPENDENCE AVE, S.W.
Washington DC 20201

8. NAME AND ADDRESS OF CONTRACTOR *(No., street, county, State and ZIP Code)*

CYTOVALE INC 1535473
Attn: (b) (6)
150 EXECUTIVE PARK BLVD STE 4100
SAN FRANCISCO CA 941343322

CODE 1535473 FAC LITY CODE

(x) 9A. AMENDMENT OF SOLICITATION NO.

9B. DATED *(SEE ITEM 11)*

x 10A. MODIFICATION OF CONTRACT/ORDER NO. 75A50119C00072

10B. DATED *(SEE ITEM 13)* 09/28/2019

11. THIS ITEM ONLY APPLIES TO AMENDMENTS OF SOLICITATIONS

☐ The above numbered solicitation is amended as set forth in Item 14. The hour and date specified for receipt of Offers ☐ is extended ☐ is not extended.
Offers must acknowledge receipt of this amendment prior to the hour and date specified in the solicitation or as amended , by one of the following methods: (a) By completing tems 8 and 15, and returning _____ copies of the amendment; (b) By acknowledging receipt of this amendment on each copy of the offer submitted ; or (c) By separate letter or electronic communication which includes a reference to the solicitation and amendment numbers. FAILURE OF YOUR ACKNOWLEDGEMENT TO BE RECEIVED AT THE PLACE DESIGNATED FOR THE RECEIPT OF OFFERS PRIOR TO THE HOUR AND DATE SPECIFIED MAY RESULT IN REJECTION OF YOUR OFFER. If by virtue of this amendment you desire to change an offer already submitted , such change may be made by letter or electronic communication, provided each letter or electronic communication makes reference to the solicitation and this amendment, and is received prior to the opening hour and date specified.

12. ACCOUNT NG AND APPROPRIATION DATA *(If required)*
2020.1992020.25106 Net Increase: $3,833,363.00

13. THIS ITEM ONLY APPLIES TO MODIFICATION OF CONTRACTS/ORDERS. IT MODIFIES THE CONTRACT/ORDER NO. AS DESCRIBED IN ITEM 14.

CHECK ONE	
	A. THIS CHANGE ORDER IS ISSUED PURSUANT TO: *(Specify authority)* THE CHANGES SET FORTH IN ITEM 14 ARE MADE IN THE CONTRACT ORDER NO. IN ITEM 10A.
	B. THE ABOVE NUMBERED CONTRACT/ORDER IS MODIF ED TO REFLECT THE ADM NISTRATIVE CHANGES *(such as changes in paying office, appropriation data, etc.)* SET FORTH N ITEM 14, PURSUANT TO THE AUTHORITY OF FAR 43.103(b).
	C. THIS SUPPLEMENTAL AGREEMENT IS ENTERED INTO PURSUANT TO AUTHORITY OF:
X	D. OTHER *(Specify type of modification and authority)* FAR 43.103(a) & FAR 43.204

E. IMPORTANT Contractor ☐ is not ☒ is required to sign this document and return _____ copies to the issuing office.

14. DESCRIPTION OF AMENDMENT/MODIFICATION *(Organized by UCF section headings, including solicitation/contract subject matter where feasible.)*

Tax ID Number: 45-4784004
DUNS Number: 078418950
Delivery Location Code: HHS
HHS
200 Independence Avenue, SW
Washington DC 20201 US

Appr. Yr.: 2020 CAN: 1992020 Object Class: 25106
Period of Performance: 09/30/2019 to 05/15/2021

Change Item 2 to read as follows(amount shown is the obligated amount):
Continued ...

Except as provided herein, all terms and conditions of the document referenced in Item 9 A or 10A, as heretofore changed, remains unchanged and in full force and effect.

15A. NAME AND TITLE OF SIGNER *(Type or print)*		16A. NAME AND TITLE OF CONTRACT NG OFFICER *(Type or print)*	
		(b) (6)	
15B. CONTRACTOR/OFFEROR	15C. DATE SIGNED	16B. UNITED STATES OF AMERICA	16C. DATE SIGNED
(Signature of person authorized to sign)		*(Signature of Contracting Officer)*	

NAME OF OFFEROR OR CONTRACTOR
CYTOVALE INC 1535473

ITEM NO. (A)	SUPPL ES/SERVICES (B)	QUANTITY (C)	UNIT (D)	UNIT PRICE (E)	AMOUNT (F)
2	Performing R&D services in support of the execution of SeptiScan analytical and clinical validation, and preparation for regulatory submission Reports and other deliverables. Obligated Amount: $3,410,194.00 Delivery: 360 Days After Award Change Item 3 to read as follows(amount shown is the obligated amount):				3,410,194.00
3	Performing R&D services related to securing the SeptiScan supply chain and preparing for manufacturing scale up and validation Reports and other deliverables. Obligated Amount: $423,169.00 Delivery: 100 Days After Award Please see "Description of Changes"				423,169.00

As referenced in SECTION SF 30 BLOCK 14

DESCRIPTION OF CHANGES:

The purpose of this modification is to:

1) Exercise CLIN 002: Execute Analytical and Clinical Validation, and Prepare for Regulatory Submission, Period of Performance March – December 2020; Change POP date and Revise Budget.

CLIN	Description	Period of Performance	Estimated Total Cost	Estimated Contractor Cost-Share (35%)	Estimated Government Cost
002	Performing R&D services in support of the execution of SeptiScan analytical and clinical validation, and preparation for regulatory submission Reports and other deliverables.	April 7, 2020 through May 15, 2021	$5,246,453	$1,836,259	$3,410,194

2) Exercise CLIN 003: Secure Supply Chain and Prepare for Manufacturing Scale Up and Validation Period of Performance April - October 2020; Change POP date and Revise Budget.

003	Performing R&D services related to securing the SeptiScan supply chain and preparing for manufacturing scale up and validation Reports and other deliverables.	April 7, 2020 through December 15, 2020	$651,029	$227,860	$423,169

3) Revise Section J: Statement of Work to show as follows:

Attachment 2 – Amendment 1

Biomedical Advanced Research and Development Authority (BARDA)
Special Instruction under DRIVe Broad Agency Announcement

Project Title: Development of the SeptiScan Program

Contractual Statement of Work
April 7, 2020

A. STATEMENT OF WORK

PREAMBLE

Independently, and not as an agent of the government, Cytovale shall furnish all necessary services; qualified professional, technical, and administrative personnel; and material, equipment, and facilities not otherwise provided by the government under the terms of this contract, as needed to perform the tasks set forth below.

The government reserves the right to modify the budget, progress, schedule, or milestones to add or delete processes, schedules, or deliverables if the need arises. Because of the nature of this research and development (R&D) contract and the complexities inherent in this and prior programs, at designated milestones the government will evaluate whether work should be redirected or removed, or whether schedule or budget adjustments should be made. The government reserves the right to change the product, process, schedule, or events to add or delete part or all of these elements as the need arises.

Overall Objectives and Scope

The overall objective of this contract is to complete the product development of the SeptiScan Program and seek regulatory clearance for the SeptiScan System.

The scope of work for this contract includes product, manufacturing and supply chain development of the SeptiScan instrument modules, accessories, and consumables, analytical and clinical design validation of the SeptiScan System performance on production equivalent units in multi-site studies, preparation of the FDA 510(k) pre-market submission package for submission and anticipated regulatory clearance, and launch preparations including manufacturing process validation at commercial scale.

The scope of work is broken into the following 5 CLIN phases:

- CLIN 1: Product and Manufacturing Development to Design Freeze, and Design Verification and Validation Preparation
- CLIN 2: Execute Analytical and Clinical Validation, and Prepare for Regulatory Submission
- CLIN 3: Secure Supply Chain and Prepare for Manufacturing Scale Up and Validation
- CLIN 4: Complete Regulatory Submission and Obtain FDA 510(k) Regulatory Clearance
- CLIN 5: Finalize Manufacturing Readiness for Launch

CLIN 1: PRODUCT AND MANUFACTURING DEVELOPMENT TO DESIGN FREEZE, AND DESIGN VERIFICATION AND VALIDATION PREPARATION

CLIN 1 is in support of the Development Stage Gate. The completion of all the AIMs and associated deliverables in this CLIN are required to formally exit the development stage and support design verification and validation activities. Briefly, AIM 1 is focused on design documentation to capture decisions made about the design with respect to requirements. In AIM 2, the focus is on the final generalization testing of the classification SeptiScan Algorithm,

locking the SeptiScan Algorithm for the validation study and obtaining feedback on the user interface. In AIM 3, the transfer of the design to manufacturing is initiated to generate pilot units and then production equivalent units, which will be used in formal Design Verification and Validation. The delivery of pilot systems and consumables to Cytovale will serve as an approval trigger for CLIN 2 (CLIN 2 Go/No-go Milestones). Subsequently, the Design Freeze and Development Stage Gate Review minutes, with accompanying design review materials (i.e. approval materials documenting the readiness of the SeptiScan System to enter the Design Verification Stage), will serve as one of the approval go/no-go Milestone for CLIN 3 (CLIN 3 Go/No-Go Milestone #1). Finally AIM 4 will focus on preparation of the design verification and validation studies, the dry runs, and formal execution of the analytical performance and clinical validation studies that will be the focus of CLIN 2. First IRB approvals obtained for the analytical validation and clinical validation studies will serve as a third approval go/no-go Milestone for CLIN2 (CLIN 2 Go/No-Go Milestone #3).

Proposed Period of Performance: September 2019 – December 2020

AIM 1: Complete Engineering Design Optimization of the SeptiScan System and Freeze Requirements

This aim seeks to integrate the learnings from the Beta Clinical Study and implement necessary design improvements for the SeptiScan System modules, software, and consumables (i.e. reagents, controls, and cartridge). The improved system design, its usability, and performance, including preliminary short-term reagent stability studies, will be assessed against target specifications through non-clinical and clinical engineering studies ahead of design freeze, on prototypes, pilots, and production equivalent units. (b) (4) [redacted]

Objective: Demonstrate SeptiScan System design engineering readiness and lock design input requirements ahead of design freeze – AIM 1 is performed concurrently with AIMs 2, 3 and 4.

AIM 1 Tasks/WBS:

1.1 Program Management (WBS 1.1) – supports all AIMS in CLIN 1

1.1.1 Technical and Contractual Project Management (WBS 1.1.1).

- The overall management, integration, and coordination of all contract activities, including a technical and administrative infrastructure to ensure the efficient planning, initiation, implementation, and direction of all contract activities;
- A principal investigator (PI) or project manager (PM) responsible for project management, communication, tracking, monitoring, and reporting on status, progress, and modification to the project requirements and timelines, including projects undertaken by subcontractors. The contract deliverables list identifies all contract deliverables and reporting requirements for this contract;
- A project manager with responsibility for monitoring and tracking day-to- day progress and timelines; coordinating communication and project activities; costs incurred; and program management. The contract deliverables list identifies all contract deliverables and reporting requirements for this contract;
- A BARDA liaison with responsibility for effective communication with the Contracting Officer (CO) and Contracting Officer's Representative (COR). The liaison may be the PM;
- Administrative and legal staff capability with responsibility for developing compliant subcontracts, consulting, and other legal agreements; ensuring timely acquisition of all

proprietary rights, including intellectual property (IP) rights; and reporting all inventions made in the performance of the contract;

- Administrative staff capability with responsibility for financial management and reporting on all activities conducted by the contractor and any subcontractors;
- Contract Review Meetings:
  - The contractor shall participate in regular meetings to coordinate and oversee the contract effort conjointly with the CO and COR. Such meetings may include, but are not limited to, meeting of the contractors and subcontractors to discuss clinical manufacturing progress, product development, product assay development, scale-up manufacturing development, clinical sample assays development, preclinical/clinical study designs and regulatory issues; meetings with individual contractors and other government officials to discuss the technical, regulatory, and ethical aspects of the program; and meetings with technical consultants to discuss technical data provided by the contractor;
  - The contractor shall participate in teleconferences every month with the CO and COR to discuss the performance of the contract, unless otherwise directed. Teleconferences or additional face-to-face meetings may be more frequent at the request of the CO.
- Gantt Chart
  - Within 30 calendar days of the effective date of the contract, the contractor shall submit a first draft of an updated Gantt Chart to the CO and COR for review and comment. The Gantt Chart shall be incorporated into the contract and will be used to monitor performance of the contract. The contractor shall include the key milestones and Go/No-Go Milestones.
  - Project Management Plan: In the management of this contract, the contractor shall utilize Project Progress Management tools/techniques to track and monitor the cost and schedule of the project. The contractor and the government agree that at a minimum, the contractor shall utilize the cost and schedule tools/techniques in the contract deliverable for project management purposes. The contractor shall submit the project progress management report to the CO and COR on a monthly basis.
- Monthly Reports: *If requested, the contractor shall deliver Project Status Reports on a monthly basis. The reports shall address the items below cross referenced to the SOW, or other Project Management Plan tool(s):*
  i. Executive summary highlighting the progress, issues, and relevant manufacturing, engineering/non-clinical, clinical, and regulatory activities;
  ii. Progress in meeting contract milestones, detailing the planned progress and actual progress during the reporting period, explaining any differences between the two and corrective steps;
  iii. Updated Risk Management Plan (every three months);
  iv. Three-month rolling forecast of planned activities;
  v. Progress of regulatory submissions

1.1.2 Risk Management (WBS 1.1.2)

Develop a Risk Management Plan within 90 days of contract award highlighting potential problems and/or issues that may arise during the life of the contract; their impact on cost, schedule, and performance; and appropriate remediation plans. This plan should reference relevant WBS elements where appropriate. Updates to this plan shall be included, at a minimum, on a quarterly basis (every three months) in the monthly Project Status Report.

1.1.3 Subcontractors Management (WBS 1.1.3)

Manage subcontractors and consultants providing specific contracted services informing the development of, or manufacturing materials for the SeptiScan program for the timely

completion of program deliverables.

1.1.4 Data Management (WBS 1.1.4)

i. Develop and implement data management and quality control systems/procedures, including transmission, storage, confidentiality, and retrieval of all contract data;
ii. Provide for the statistical design and analysis of data resulting from the research; and
iii. Provide raw data or specific analyses of data generated with contract funding to the CO and COR, upon request.
iv. Prepare journal and conference publications in support of dissemination of key program findings.

1.2 Engineering (WBS 1.2)

1.2.1 SeptiScan Instrument System Development (WBS 1.2.1)

Complete the design improvements and development of the SeptiScan System instrument modules (SPM, CYM, IAM modules) hardware, software, and packaging.

1.2.2 SeptiScan Consumables Development (WBS 1.2.2)

Complete the development of SeptiScan System Consumables (cartridges, reagents, external controls), including primary and secondary packaging labeling.

1.2.3 Engineering non-clinical studies (WBS 1.2.3)

Design hardware and software pre-verification activities and human factor evaluations assessing hardware, software engineering readiness and usability of the SeptiScan System instrument and modules.

1.7 Quality Assurance (WBS 1.7) – supports all AIMS in CLIN 1

1.7.1 Quality Management (WBS 1.7.1)

Manage compliance to quality system processes and procedures, approve documentation and change controls, and manage the SeptiScan System Device History File.

1.7.2 Subcontractors Compliance Management (WBS 1.7.2)

Qualify and manage vendors' related quality processes, audit critical vendors per audit schedule.

AIM 2: Freeze SeptiScan System Algorithm and Confirm Suitability of System User Interface.

This aim seeks to initiate a naïve study site (b) (4) to test and lock the SeptiScan Algorithm prior to evaluating patients in the formal Clinical Validation Study, where a parallel objective is to test and provide feedback on the SeptiScan System user interface with intended users in an intended environment. In support of these objectives, we are proposing to collect and process (b) (4) samples at a naïve clinical laboratory site operated by non-Cytovale intended users / laboratory operators using the SeptiScan intended user Graphical User Interface (GUI) workflow. This additional testing will provide insights into the generalization of the SeptiScan Algorithm and offer a chance to get direct feedback from intended users on the SeptiScan System user interface as they operate the instrument to process the samples. User feedback will be collected through a survey. Results will be compared to our released user needs document [redacted]. Any changes will be incorporated in GUI designs prior to the design freeze. The SeptiScan (b) (4) results from this naïve site study will be reviewed to assess performance prior to freezing algorithm parameters, performance metrics, and cutoffs as part of the formal Design Freeze process.

Objective: Finalize and document the SeptiScan Algorithm and obtain intended user feedback

on the System user interface.

AIM 2 Tasks/WBS:

1.1. Program Management (WBS 1.1) – supports all AIMS in CLIN 1

Program management scope in AIM 2 is consistent with program management scope in AIM 1.

1.3 Data Management & Biostatistics (WBS 1.3)

1.3.1 Algorithm / Diagnostic Model Development (WBS 1.3.1)

Perform data analysis and pre-verification of algorithm parameters and report performance obtained from the non-clinical engineering studies and naïve clinical site study, as wells as performance metrics and proposed cut offs for the clinical validation study.

1.4 Clinical (WBS 1.4)

1.4.1 Naïve Clinical Site Study (WBS 1.4.1)

Clinical operations to support enrollment at a naïve clinical site for collection and processing of (b) (4) samples using the intended use workflow in support of assessing instrument user interface, user feedback, and clinical operation logistics.

1.7 Quality Assurance (WBS 1.7) – supports all AIMS in CLIN 1

1.7.1 Quality Management (WBS 1.7.1)

Manage compliance to quality system processes and procedures, approve documentation and change controls, and manage the SeptiScan System Device History File.

1.7.2 Subcontractors Compliance Management (WBS 1.7.2)

Qualify and manage vendors' related quality processes, audit critical vendors per audit schedule.

AIM 3: Transfer Design and Manufacture Production Equivalent Investigational Use Only Instruments and Consumables

This aim focuses on initiating the transfer of the design to contract manufacturers and locking the requirements before building and evaluating the first production equivalent instruments and consumables at low volume scale. Pilot Investigational Use Only (IUO) instruments and consumable lots, followed by Production Equivalent instruments and consumable lots will be used under AIM 1 to assess the maturity of the overall design (including hardware, software, and user interface) ahead of design freeze. In parallel, we will begin securing the product supply chain by negotiating contract manufacturing services, supply agreements, and quality agreements with key vendors.

Objective: To build and evaluate the production equivalent SeptiScan instruments and consumables pilot lots ahead of design freeze and work towards securing the SeptiScan supply chain.

AIM 3 Tasks/WBS:

1.1 Program Management (WBS 1.1) – supports all AIMS in CLIN 1

Program management scope in AIM 3 is consistent with program management scope in AIM 1.

1.5 Manufacturing Operations (WBS 1.5)

1.5.1 Contract Manufacturer (CM) Production Equivalent IUO SeptiScan Instrument Manufacturing (WBS 1.5.1)

Transfer the SeptiScan Instrument and modules design to the CM, develop and manage the associated instrument supply chain, develop the manufacturing assembly, test procedures and acceptance criteria, dry run manufacturing assembly and release process through the build of pilot instruments, and subsequently build up to 10 Investigational Use Only (IUO) production equivalent SeptiScan units for use in formal V&V.

1.5.2 CM Production Equivalent IUO SeptiScan Consumables Manufacturing (WBS 1.5.2)

Transfer the SeptiScan consumables (cartridge, reagents, controls, packaging) design to contract manufacturers, develop and manage the associated supply chain, develop the manufacturing assembly, test procedures and acceptance criteria. Build and release Pilot IUO SeptiScan Consumable lots of cartridges (minimum of 350 units per lot), reagents (minimum of 50 units per lot), and external controls (minimum of 35 units per lot). Build and release production equivalent IUO SeptiScan Consumable lots for use in V&V.

1.7 Quality Assurance (WBS 1.7) – supports all AIMS in CLIN 1

1.7.1 Quality Management (WBS 1.7.1)

Manage compliance to quality system processes and procedures, approve documentation and change controls, and manage the SeptiScan System Device History File.

1.7.2 Subcontractors Compliance Management (WBS 1.7.2)

Qualify and manage vendors' related quality processes, audit critical vendors per audit schedule.

AIM 4: Readiness to initiate Pilot Analytical Performance & Clinical Pre-Validation Studies

This aim seeks to complete the preparations for piloting device engineering design verification, analytical performance pre-validation and clinical pre-validation studies. Activities will include preparing analytical and clinical validation plans and protocols per FDA pre-submission feedback (Q160124 #S002), qualifying and contracting a clinical and laboratory site to execute the clinical pre-validation study, designing formal clinical study protocols in support of analytical performance and clinical validation studies, submitting all relevant protocols and Informed Consent Forms for IRB approval, preparing all studies documentation and binders, completing site initiation visits, system installation and operators training at the pre-validation clinical site.

Objectives: Complete all necessary activities to allow for piloting device design engineering pre-verification studies, analytical performance pre-validation and clinical pre-validation studies.

AIM 4 Tasks/WBS:

1.1 Program Management (WBS 1.1) – supports all AIMS in CLIN 1

Program management scope in AIM 4 is consistent with program management scope in AIM 1.

1.2 Engineering (WBS 1.2)

1.2.4 Prepare for design verification and validation (WBS 1.2.4)

Develop verification and validation plans, engineering verification protocols (HW, SW),

analytical performance study protocols, test methods work instructions, and user training documentation.

1.2.5 Field Engineering (WBS 1.2.5)

SeptiScan System installation and qualifications at clinical laboratory site(s), laboratory operators training, instrument services and repairs, preventive maintenance.

1.3 Data Management & Biostatistics (WBS 1.3)

1.3.2 Prepare for design verification and validation (WBS 1.3.2)

Develop processes and plans for data collection, data monitoring, and database management at the clinical pre-validation site. Develop analytical performance study protocols, and statistical analyses plans for verification and validation studies.

1.4 Clinical (WBS 1.4)

1.4.2 Prepare for analytical performance, healthy reference range, and clinical validation studies (WBS 1.4.2)

Identification, selection, and contracting of clinical site and clinical laboratory for enrolling and executing the clinical pre-validation study. Develop study protocols and ICFs for the Analytical Validation, the Healthy Reference Range and Clinical Validation Studies, seeking IRB approval for study protocols, and preparing the clinical data management plan.

1.6 Regulatory (WBS 1.6)

1.6.1 Update Regulatory Strategy (WBS 1.6.1)

Review and update the regulatory strategy of the SeptiScan System as needed based on FDA feedback obtained at the Q160124 S001 and S002 pre-submission meetings or other input changes.

1.6.2 FDA Communications (WBS 1.6.2)

i. Engage the Food and Drug Administration (FDA) on a path to support the use of the product for the specific indication, including submitting pre-submission supplements as needed.
ii. Prepare materials for and requesting, scheduling, and participating in all meetings with the FDA, including meetings to review all data packages; and
iii. Provide BARDA with (i) the initial draft minutes and final draft minutes of any formal meeting with the FDA, and (ii) final draft minutes of any informal meeting with the FDA.

1.6.3 Labeling (WBS 1.6.3)

Prepare Investigational Use Only - Instruction for Use, Package Insert and User Manual documentation for use at the clinical site executing clinical pre-validation studies.

1.7 Quality Assurance (WBS 1.7) – supports all AIMS in CLIN 1

1.7.1 Quality Management (WBS 1.7.1)

Manage compliance to quality system processes and procedures, approve documentation and change controls, and manage the SeptiScan System Device History File.

1.7.2 Subcontractors Compliance Management (WBS 1.7.2)

Qualify and manage vendors' related quality processes, audit critical vendors per audit schedule.

CLIN 2: EXECUTE ANALYTICAL & CLINICAL VALIDATION, AND PREPARE FOR

REGULATORY SUBMISSION

CLIN 2 will focus first on executing pre-clinical, pre-verification, and pre-analytical validation assessments of the SeptiScan System and consumables and integrate the learnings from executing these pilot studies to reduce the risk to formal V&V. It will then be followed by the formal execution of design verification, analytical validation, and clinical validation activities. It will also focus on preparing the 510(k) regulatory study package as data becomes available. The initiation of CLIN 2 will be dependent upon the successful completion of the approval go/no go milestone(s) in CLIN 1.

Proposed Period of Performance: April 2020 – March 2021

AIM 12: Execute Pre-Validation Clinical Pilot Studies, Engineering Pre-Verification, and Analytical Performance Pre-Validation Studies, and Achieve Readiness to Enroll FPI in Formal V&V.

This AIM will focus on assessing the performance of the CM SeptiScan System and consumables in a pre-verification and pre-validation setting. Pilot SeptiScan instruments and consumables (cartridges, reagents), and subsequently when available Production Equivalent instruments and consumables, will be used to dry-run the engineering verification, analytical validation and clinical validation studies ahead of the formal Verification and Validation studies. This AIM will also evaluate the revised instrument user interface incorporating recommended improvements determined under AIM2/CLIN1 and improve device labeling. Dry-running engineering verification and analytical validation studies will enable assessing the practicality of proposed formal protocols and initial results obtained when running the protocol or a truncated version of the protocol where relevant. Verification and validation protocols will be revised as needed based on the outcomes of the dry-runs. Two clinical pre-validation pilot studies will be performed at contracted clinical sites. One pilot study will target the intended population presenting to the ED with broad suspicion of sepsis as prepared for under AIM 4/CLIN1. A second pilot study will target a specific cohort of patients suspected of respiratory infections (including SARS-CoV-2 infection) presenting to the ED. Activities to support these pilot studies will include the build of two additional manufacturing pilot SeptiScan instruments by the CM, as well as all clinical operations activities necessary to enable patient enrollment under the second pilot study (clinical protocol development, IRB approval, study binders, systems installation and operational qualification, operators training, and SIV, etc.). System and algorithm readiness will be captured through documentation and technical review ahead of the launch of the studies to test the established sepsis algorithm in these patient cohorts, and the respiratory infection cohort is expected to provide insight into the algorithm's performance in cases of sepsis due to viral infection.

Additionally, activities will focus on achieving clinical operational readiness to initiate formal V&V with final selection and contracting of clinical validation sites, submitting all relevant protocols and ICFs for site IRB approvals, preparing studies documentation and binders, and completing at least one site initiation visit, system installation and training of operators at one of the clinical labs that will be executing the analytical performance and clinical validation studies. At the end of this AIM, a Clinical Operations Readiness Review will be held to demonstrate readiness to enroll in the analytical and clinical validation studies.

Objective: De-risk formal design analytical and clinical validation by completing pre-V&V dry runs and pilot studies in intended settings, and achieve clinical operation readiness to initiate enrollment to support formal analytical performance and clinical validation studies.

AIM12 Tasks/WBS:

2.1 Program Management (WBS 2.1) – supports all AIMS in CLIN 2

Program management scope in CLIN 2 - AIM 12 is consistent with program management scope in CLIN 1 - AIM 1.

2.2 Engineering (WBS 2.2)

2.2.1 Execute components and system modules engineering design pre-verification (WBS 2.2.1)

Execute component and system modules engineering design pre-verification per released verification protocols, review results in technical reviews and update protocols as needed. Validate test methods as applicable.

2.2.2 Execute SeptiScan System analytical performance pre-validation studies (WBS 2.2.2)

Execute the SeptiScan System analytical performance pre-validation, pilot, and stability studies per released protocols, review results in technical reviews and update protocols as needed.

2.2.3 Field Engineering (WBS 2.2.3)

SeptiScan System installation and qualifications at the clinical laboratory site(s), laboratory operators training, instrument services and repairs, preventive maintenance.

2.3 Data Management & Biostatistics (WBS 2.3)

2.3.1 Execute Pilot Studies Data Analysis (WBS 2.3.1)

In support of engineering pre-verification, analytical performance pre-verification, and clinical pre-validation studies (aka Pilot studies): implementation and execution of the data collection plan, data storage plan, data monitoring plan, evaluation of the statistical analyses as per statistical analysis plan, aggregate data points per study, evaluate statistical acceptance criteria, construction of tables as per primary and secondary objectives, and reporting of key findings in Technical Reviews.

2.3.2 Readiness for Formal Verification and Validation (WBS 2.3.2)

Improve or revise processes and plans as necessary for data monitoring and database management ahead of formal V&V execution; revise analytical performance study protocols and statistical analyses if necessary, validate tools (including electronic data capture tools) and test methods as applicable.

2.4 Clinical (WBS 2.4)

2.4.1 Execute Analytical and Clinical Pre-Validation Studies (WBS 2.4.1)

Initiate enrollment for the Analytical and Clinical Pre-Validation Pilot Studies; communicate with sites to maintain commitment to enrollment and data quality, provide regular updates and monitor sites for compliance as planned. Manage study material inventory to sites. Manage the Trial Master File (TMF). (b) (4) [redacted] Support the verification and lock of the study databases and prepare clinical analyses.

2.4.2 Readiness for Formal Analytical Performance, Healthy Reference Range, and Clinical Validation Studies (WBS 2.4.2)

Identify, qualify, and contract selected clinical sites and clinical laboratories for enrolling

and executing the formal analytical, healthy reference range and clinical validation studies. Seek site IRB approvals for the different study protocols at the different sites, prepare the clinical data management plan, develop study binders, and complete site initiation visits.

2.4.4 Prepare for Pilot Study #2 (Respiratory Cohort)
Identification, selection, and contracting of clinical site and clinical laboratory for enrolling the second clinical pilot study. Development of the study protocol, seeking IRB approval for the study protocol, and preparing the clinical data management plan.

2.5 Manufacturing Operations (WBS 2.5)

2.5.1 Contract Manufacturer (CM) IUO SeptiScan Instrument Manufacturing (WBS 2.5.1)
Build an additional 2 Investigational Use Only (IUO) SeptiScan Instrument units for use in pilot studies and later in formal V&V.

2.5.2 CM IUO SeptiScan Consumables Manufacturing (WBS 2.5.2)
Transfer the SeptiScan consumables (cartridge, reagents, controls, packaging) design to contract manufacturers, develop and manage the associated supply chain, develop the manufacturing assembly, test procedures and acceptance criteria for the production equivalent lots. Build and release pilot and production equivalent IUO SeptiScan Consumable lots of cartridges (minimum of 350 units per lot), reagents (minimum of 50 units per lot), and external controls (minimum of 35 units per lot).

2.6 Regulatory (WBS 2.6)

2.6.1 Labeling for Formal Verification and Validation (WBS 2.6.1)
Prepare Investigational Use Only Draft Labelling - Instruction for Use, Package Insert and User Manual documentation per 21CFR809.10(b) for use in the formal analytical and clinical validation studies.

2.7 Quality Assurance (WBS 2.7) – supports all AIMS in CLIN 2

2.7.1 Quality Management (WBS 2.7.1)
Manage compliance to quality system processes and procedures, approve documentation and change controls, and manage the SeptiScan System Device History File.

2.7.2 Subcontractor Compliance Management (WBS 2.7.2)
Qualify, manage vendors' related quality processes, audit critical vendors per audit schedule.

AIM 5: Execute Formal Engineering Design Verification and Analytical Performance Studies

This aim seeks to execute and complete the formal engineering design verification and analytical performance validation for the SeptiScan System on GMP production equivalent units and consumables. It will focus on the execution of system and modules design verification activities, initiation of long-term stability studies for reagent and cartridge consumables (per CLSI EP25 guidance), and execution of analytical validation studies per the study design discussed and agreed upon with FDA. Due to their specific design, analytical validation studies will be executed concurrently to the clinical validation studies described in AIMs 6 and 7. This aim will also support the execution of all the studies through study materials inventory management (i.e. manufacturing of additional consumable lots as needed and shipping to study

sites).

Objective: Complete SeptiScan formal design verification, analytical validation, and interim long-term stability testing to use in FDA 510(k) submission.

AIM 5 Tasks/WBS:

2.1 Program Management (WBS 2.1) – supports all AIMS in CLIN 2

Program management scope in CLIN 2 - AIM 5 is consistent with program management scope in CLIN 1 - AIM 1.

2.2 Engineering (WBS 2.2)

2.2.3 Field Engineering (WBS 2.2.3)

SeptiScan System installation and qualifications at the clinical laboratory sites, laboratory operators training, instrument services and repairs, preventive maintenance.

2.2.4 Execute components and system modules formal engineering design verification (WBS 2.2.4)

Execute component and system modules engineering design verification and validation per approved verification protocols and prepare reports.

2.2.5 Execute SeptiScan System formal analytical performance studies (WBS 2.2.5)

Execute the SeptiScan System analytical performance validation and stability studies per their approved protocols and prepare reports.

2.3 Data Management & Biostatistics (WBS 2.3)

2.3.3 Execute Formal Verification and Validation Data Analysis (WBS 2.3.3)

In support of analytical performance studies, healthy reference range study, and clinical validation study: collect data, monitor data, perform analyses, aggregate data points per study, evaluate statistical acceptance criteria, report key findings and construct tables as per primary and secondary objectives.

2.4 Clinical (WBS 2.4)

2.4.3 Execute Formal Analytical Performance Validation, Healthy Reference Range, and Clinical Validation Studies (WBS 2.4.3)

Initiate enrollment for the Analytical Performance Validation, Healthy Reference Range, and Clinical Validation Studies; communicate with sites to maintain commitment to enrollment and data quality, provide regular updates and monitor sites for compliance as planned. Manage study material inventory to sites. Manage the Trial Master Files (TMF). (b) (4) Support the verification and lock of the study databases and prepare clinical analyses.

2.5 Manufacturing Operations (WBS 2.5)

2.5.2 CM IUO SeptiScan Consumables Manufacturing (WBS 2.5.2)

Transfer the SeptiScan consumables (cartridge, reagents, controls, packaging) design to contract manufacturers, develop and manage the associated supply chain, develop the manufacturing assembly, test procedures and acceptance criteria for the production equivalent lots. Build and release pilot and production equivalent IUO SeptiScan Consumable lots of cartridges (minimum of 350 units per lot), reagents (minimum of 50 units per lot), and external controls (minimum of 35 units per lot).

2.7 Quality Assurance (WBS 2.7) – supports all AIMS in CLIN 2

2.7.1 Quality Management (WBS 2.7.1)

Manage compliance to quality system processes and procedures, approve documentation and change controls, and manage the SeptiScan System Device History File.

2.7.2 Subcontractor Compliance Management (WBS 2.7.2)

Qualify, manage vendors' related quality processes, audit critical vendors per audit schedule.

AIM 6: Execute Formal Healthy Reference Range Study

This aim seeks to execute the SeptiScan System Healthy Reference Range Study. This study will enroll (b) (4) healthy subjects donating blood (b) (4) with close proximity to a lab where the assays can be performed. Healthy subjects will span the demographic groups (e.g., age, race, ethnicity, and gender) found in the clinical validation study (AIM 7). Subjects will be analyzed as a cohort and results will be summarized. Key activities under this aim include initiating the Healthy Reference Range study at qualified sites, monitoring data, and completing enrollment. Successful completion of this phase will be marked by the release of the reference range study report.

Objective: Complete the Healthy Reference Range Study for use in the FDA 510(k) submission.

AIM 6 Tasks/WBS:

2.1 Program Management (WBS 2.1) – supports all AIMS in CLIN 2

Program management scope in CLIN 2 - AIM 6 is consistent with program management scope in CLIN 1 - AIM 1.

2.2 Engineering (WBS 2.2)

2.2.3 Field Engineering (WBS 2.2.3)

All remaining SeptiScan System installation and qualifications at the clinical laboratory sites, laboratory operators training, instrument services and repairs, preventive maintenance.

2.3 Data Management & Biostatistics (WBS 2.3)

2.3.3 Execute Formal Verification and Validation Data Analysis (WBS 2.3.3)

In support of analytical performance studies, healthy reference range study and clinical validation study: collect data, monitor data, perform analyses, aggregate data points per study, evaluate statistical acceptance criteria, report key findings and construct tables as per primary and secondary objectives.

2.4 Clinical (WBS 2.4)

2.4.3 Execute Formal Analytical Performance Validation, Healthy Reference Range, and Clinical Validation Studies (WBS 2.4.3)

Initiate enrollment for the Analytical Performance Validation, Healthy Reference Range, and Clinical Validation Studies; communicate with sites to maintain commitment to enrollment and data quality, provide regular updates and monitor sites for compliance as

planned. Manage the Trial Master Files (TMF). (b) (4) [redacted] Support the verification and lock of the study databases and prepare clinical analyses.

2.7 Quality Assurance (WBS 2.7) – supports all AIMS in CLIN 2

2.7.1 Quality Management (WBS 2.7.1)
Manage compliance to quality system processes and procedures, approve documentation and change controls, and manage the SeptiScan System Device History File.

2.7.2 Subcontractor Compliance Management (WBS 2.7.2)
Qualify, manage vendors' related quality processes, audit critical vendors per audit schedule.

AIM 7: Execute Formal Clinical Validation Study

This aim seeks to execute the SeptiScan System formal Design Clinical Validation Study, (b) (4) [redacted] Key activities include initiating the clinical study at qualified sites, monitoring data, commencing and completing enrollment of multi-site, multi-hundred patient clinical study (b) (4) [redacted] to achieve our primary and secondary study objectives. Successful completion of this phase will be marked by the release of the clinical validation final analysis for 510(k) filing.

Objective: Complete the multi-site SeptiScan Clinical Validation Study for use in the FDA 510(k) submission.

AIM 7 Tasks/WBS:

2.1 Program Management (WBS 2.1) – supports all AIMS in CLIN 2
Program management scope in CLIN 2 - AIM 7 is consistent with program management scope in CLIN 1 - AIM 1.

2.2 Engineering (WBS 2.2)

2.2.3 Field Engineering (WBS 2.2.3)
All remaining SeptiScan System installation and qualifications at the clinical laboratory sites, laboratory operators training, instrument services and repairs, preventive maintenance.

2.3. Data Management & Biostatistics (WBS 2.3)

2.3.3 Execute Formal Verification and Validation Data Analysis (WBS 2.3.3)
In support of the analytical performance studies, healthy reference range study, and clinical validation study: collect data, monitor data, perform analyses, aggregate data points per study, evaluate statistical acceptance criteria, report key findings and construct tables as per primary and secondary objectives.

2.4. Clinical (WBS 2.4)

2.4.3 Execute Formal Analytical Performance Validation, Healthy Reference Range, and Clinical Validation Studies (WBS 2.4.3)
Initiate enrollment for the Analytical Performance Validation, Healthy Reference Range, and Clinical Validation Studies; communicate with sites to maintain commitment to enrollment and data quality, provide regular updates and monitor sites for compliance as

planned. Manage the Trial Master Files (TMF) (b) (4) [redacted] Support the verification and lock of the study databases and prepare clinical analyses.

2.7 Quality Assurance (WBS 2.7) – supports all AIMS in CLIN 2

2.7.1 Quality Management (WBS 2.7.1)

Manage compliance to quality system processes and procedures, approve documentation and change controls, and manage the SeptiScan System Device History File.

2.7.2 Subcontractor Compliance Management (WBS 2.7.2)

Qualify, manage vendors' related quality processes, audit critical vendors per audit schedule.

AIM 8: Prepare for FDA 510(k) submission

This aim seeks to start the assembly of the necessary data and information collected under AIMS 5, 6 and 7 to prepare the SeptiScan 510(k) pre-market notification for timely submission to the FDA. An Interim regulatory review will assess that the package assembly is on track for submission at the end of 2020.

It will also include preparing materials for any additional pre-submission supplements deemed necessary post communications with FDA on Q160124 S001 and S002 and requesting, scheduling, and participating in all meetings with the FDA.

Objective: Start preparation of SeptiScan 510(k) pre-market notification.

AIM 8 Tasks/WBS:

2.1 Program Management (WBS 2.1) – supports all AIMS in CLIN 2

Program management scope in CLIN 2 - AIM 8 is consistent with program management scope in CLIN 1 - AIM 1.

2.6 Regulatory (WBS 2.6)

2.6.2. FDA Communications (WBS 2.6.2)

i. Engage the Food and Drug Administration (FDA) on a path to support the use of the product for the specific indication, including submitting pre-submission supplements as needed.
ii. Prepare materials for and requesting, scheduling, and participating in all meetings with the FDA, including meetings to review all data packages; and
iii. Provide BARDA with (i) the initial draft minutes and final draft minutes of any formal meeting with the FDA, and (ii) final draft minutes of any informal meeting with the FDA.

2.6.3 Labeling for regulatory submission (WBS 2.6.3)

Updated labeling with study data and draft claims for use in the regulatory submission.

2.6.4 510(k) Submission Package assembly (WBS 2.6.4)

Prepare the regulatory 510(k) pre-market notification package and lead the regulatory submission interim review to ensure submission is on track.

2.7 Quality Assurance (WBS 2.7) – supports all AIMS in CLIN 2

2.7.1 Quality Management (WBS 2.7.1)

Manage compliance to quality system processes and procedures, approve documentation and change controls, and manage the SeptiScan System Device History File.

2.7.2 Subcontractor Compliance Management (WBS 2.7.2)
Qualify, manage vendors' related quality processes, audit critical vendors per audit schedule.

CLIN 3: SECURE SUPPLY CHAIN AND PREPARE FOR MANUFACTURING SCALE UP AND VALIDATION

The initiation of CLIN 3 will be dependent upon the successful completion and approval of the go/no go milestones in CLIN 1 and CLIN 2.

Proposed Period of Performance: April 2020 - March 2021

AIM 9: Secure Supply Chain and Initiate GMP Manufacturing Scale Up

This aim seeks to continue and secure the product supply chain activities initiated under AIM 1 by negotiating contract manufacturing services, supply agreements, and quality agreements with selected key vendors, initiate the technical development of backup suppliers for critical components, initiate the planning and development of manufacturing scale up processes, process validation and plan for transfer to production.

Objective: Start securing supply chain for the SeptiScan product through a combination of agreements negotiations, development of backup suppliers and ensuring all CM partners will be able to manufacture product at the anticipated commercial scale.

AIM 9 Tasks/WBS:

3.1 Program Management (WBS 3.1)
Program management scope in CLIN 3 - AIM 9 is consistent with program management scope in CLIN 1 - AIM 1.

3.2 Engineering (WBS 3.2)

3.2.1 Secure supply chain (WBS 3.2.1)
Develop supply agreements and quality agreements with existing suppliers of critical components.

3.2.2 Technical development of backup suppliers of critical components (WBS 3.2.2)
Develop and qualify backup suppliers for critical components or subassemblies to reduce risks to the commercial supply chain.

3.2.3 Support manufacturing process scale up, validation, and transfer to production (WBS 3.2.3)
Provide oversight and technical expertise to CMs for the preparation of manufacturing process scale up, validation, and transfer to production.

3.3 Data Management & Biostatistics (WBS 3.3) - Reserved

3.4 Clinical (WBS 3.4) - Reserved

3.5 Manufacturing Operations (WBS 3.5)

3.5.1 CM manufacturing process scale up initiation, validation, and preparation for transfer to production (WBS 3.5.1)
CMs planning and initiation of manufacturing process scale up, validation, and planning for transfer to production.

3.6 Regulatory (WBS 3.6) – Reserved

3.7 Quality Assurance (WBS 3.7)

3.7.1 Quality Management (WBS 3.7.1)

Manage compliance to quality system processes and procedures, approve documentation and change controls, and manage the SeptiScan System Device History File.

3.7.2 Subcontractor Compliance Management (WBS 3.7.2)

Qualify, manage vendors' related quality processes, audit critical vendors per audit schedule.

CLIN 4: COMPLETE REGULATORY SUBMISSION AND OBTAIN 510(k) REGULATORY CLEARANCE

The initiation of CLIN 4 will be dependent upon the successful completion and approval of the Go/No Go milestones in CLIN 2.

Proposed Period of Performance: January 2021 – December 1st, 2021

AIM 10: Obtain 510(k) Regulatory Clearance

This aim focuses on finalizing the 510(k) package for submission to FDA and thereafter on the 510(k) review process and timely engagement with FDA to address any questions arising in relation to our regulatory submission. It will also include establishing consumables' expiration dates from real-time stability testing negotiating final claims, intended use/indication for use statement, and labeling with the Agency. It will also include preparing materials, requesting, scheduling, and participating in all meetings with the FDA.

Objective: Finalize, submit the 510(k) pre-market notification and support the 510(k) regulatory review process to obtain regulatory clearance.

AIM 10 Tasks/WBS:

4.1 Program Management (WBS 4.1)

Program management scope in CLIN 4 - AIM 10 is consistent with program management scope in CLIN 1 - AIM 1.

4.2 Engineering (WBS 4.2)

4.2.1 Complete stability studies for components expiration dating (WBS 4.2.1)

Complete on-going long term and any stability studies initiated under AIM 5 on consumables (reagents and cartridge) to enable shelf-life dating claims in the labeling.

4.3 Data Management & Biostatistics (WBS 4.3) - Reserved

4.4 Clinical (WBS 4.4)

4.4.1 Conduct clinical site close out visits (WBS 4.4.1)

Conduct clinical sites and laboratory sites close out visits.

4.5 Manufacturing Operations (WBS 4.5) - Reserved

4.6 Regulatory (WBS 4.6)

4.6.1 FDA communications (WBS 4.6.1)

i. Address the Food and Drug Administration (FDA) questions as they arise during the review process in a timely manner to support the use of the product for the specific indication and obtention of regulatory clearance letter;
ii. Prepare materials for and requesting, scheduling, and participating in all meetings with the FDA, including meetings to review all data packages; and
iii. Provide BARDA with (i) the initial draft minutes and final draft minutes of any formal meeting with the FDA, and (ii) final draft minutes of any informal meeting with the FDA.

4.6.2 510(k) Submission Package final assembly and transmittal (WBS 4.6.2)

Finalize the regulatory 510(k) pre-market notification package for submission and submit.

4.6.3 Labeling (WBS 4.6.3)

Finalize Instruction for Use, Package Insert and User Manual documentation per 21CFR809.10(b) for the final product in agreement with FDA.

4.7 Quality Assurance (WBS 4.7)

4.7.1 Quality Management (WBS 4.7.1)

Manage compliance to quality system processes and procedures, approve documentation and change controls, and manage the SeptiScan System Device History File.

4.7.2 Subcontractor Compliance Management (WBS 4.7.2)

Qualify, manage vendors' related quality processes, audit critical vendors per audit schedule.

CLIN 5: FINALIZE MANUFACTURING READINESS FOR LAUNCH

The initiation of CLIN 5 will be dependent upon the successful completion and approval of the go/no go milestones in CLIN 2 and CLIN 3.

Proposed Period of Performance: November 2020 – December 1st, 2021

AIM 11: Readiness for Launch

This aim will be initiated post completion of AIM 9 and seeks to complete the design transfer, GMP manufacturing scale up, and process validation of the SeptiScan System and consumables. Other activities in preparation for launch will include updating the launch and go-to-market plans, and establish customer processes *(e.g., order processing and fulfillment, technical support/complaints, servicing, recall management)* and post market surveillance.

Objective: Complete the SeptiScan System and consumables manufacturing scale up, process validation, and prepare for Launch.

AIM 11 Tasks/WBS:

5.1 Program Management (WBS 5.1)

Program management scope in CLIN 5 - AIM 11 is consistent with program management scope in CLIN 1 - AIM 1.

5.2 Engineering (WBS 5.2)

5.2.1 Secure supply chain (WBS 5.2.1)

Develop supply agreements and quality agreements with existing suppliers of critical components.

5.2.2 Technical development of backup suppliers of critical components (WBS 5.2.2)
Develop and qualify backup suppliers for critical components or subassemblies to reduce risks to the commercial supply chain.

5.2.3 Support manufacturing process scale up, validation, and transfer to production (WBS 5.2.3)
Provide oversight and technical expertise to CMs for the preparation of manufacturing process scale up, validation, and transfer to production.

5.3 Data Management & Biostatistics (WBS 5.3)

5.3.1 Prepare publications (WBS 5.3.1)
Prepare manuscripts presenting the analytical performance and clinical utility of the SeptiScan System obtained from the analytical and clinical validation pivotal studies.

5.4 Clinical (WBS 5.4) - Reserved

5.5 Manufacturing Operations (WBS 5.5)

5.5.1 CM manufacturing process scale up initiation, validation, and preparation for transfer to production (WBS 5.5.1)
CMs planning and initiation of manufacturing process scale up, validation, and planning for transfer to production.

5.5.2 Complete process validation and transfer to production (WBS 5.5.2)
CMs completion of manufacturing process scale up, validation, and transfer to production.

5.6 Regulatory (WBS 5.6) - Reserved

5.7 Quality Assurance (WBS 5.7)

5.7.1 Quality Management (WBS 5.7.1)
Manage compliance to quality system processes and procedures, approve documentation and change controls, and manage the SeptiScan System Device History File.

5.7.2 Subcontractor Compliance Management (WBS 5.7.2)
Qualify, manage vendors' related quality processes, audit critical vendors per audit schedule.

4) Revise Section J: Deliverable Table to show as follows:

Contract Period	**AIM#**	**WBS**	**Milestone**	**Deliverable**	**Success Criteria**	**Est. Completion Date**
CLIN1		1.1.1	Program Management Plan and updated GANTT	Program Management Plan and updated GANTT within 30 days of contract effective date	Executive Approval of Program Management Plan and Revised GANTT	Oct 2019
CLIN1		1.1.2	Program Risk Management Plan	Program Risk Management Plan	Executive Approval of Program Risk Management Plan	Nov 2019-Feb 2020

Contract Period	AIM#	WBS	Milestone	Deliverable	Success Criteria	Est. Completion Date
CLIN1	1	1.2.1, 1.2.2, 1.2.3	Technical & Design Input Review(s) records	Cytovale approved Technical Design Review(s) and Design Input Review(s) records (e.g. review meeting minutes with any relevant accompanying review materials, including Human Factor report) documenting, respectively, the performance of the SeptiScan System and consumables post design improvements from non-clinical and clinical engineering studies, and the review of the SeptiScan System design requirements ahead of design freeze	Engineering and Quality approved Technical and Design Input Review(s) records	Oct 2019 - Aug 2020
CLIN1	1	1.2.1, 1.2.2	Locked Design input Documentation	Released User Needs Requirements, Product Requirements, Hazards and Risk documents, and Trace Matrix.	Cytovale approved locked design documentation for system modules and consumables released to Cytovale's QMS	Aug 2020
CLIN1	2	1.4.1	User Feedback Report	Cytovale approved user feedback report summarizing user survey results against user needs requirements and informing on potential changes and improvements to the user interface.	Approval of survey results capturing user feedback including assessment of potential changes and improvements to the user interface.	Mar 2020
CLIN1	2	1.3.1	Algorithm Freeze Design Review	Cytovale approved Algorithm Design Freeze Review records (*e.g., review meeting minutes with any relevant accompanying review materials*) documenting the SeptiScan Algorithm Design Freeze, performance metrics with confidence intervals, and final cutoffs ahead of design freeze and validation	Data Science and Quality approval of frozen algorithm design	July 2020
CLIN1	3	1.5.1	CLIN2 approval go/no-go: Three (3) QA-Released SeptiScan Systems	Minimum of three (3) functionally tested Pilot SeptiScan Systems built and delivered to Cytovale with build and test documentation.	Delivery of three (3) SeptiScan Systems with associated documentation to Cytovale	Apr 2020

Contract Period	AIM#	WBS	Milestone	Deliverable	Success Criteria	Est. Completion Date
CLIN1	3	1.5.2	CLIN2 approval go/no-go: Two (2) QA-Released Reagents Consumables Lots	Minimum of two Pilot lots of reagents consumables (minimum of 50 units per lot) with associated documentation released to inventory by Cytovale Quality Assurance	Quality Assurance release of two (2) lots of reagents consumables to inventory with associated documentation.	Apr 2020
CLIN1	3	1.5.2	Two (2) QA-Released Cartridge Consumables Lots	Minimum of two Pilot lots of cartridge consumables (minimum of 350 units per lot) with associated documentation released to inventory by Cytovale Quality Assurance	Quality Assurance release of two (2) lots of cartridge consumables to inventory with associated documentation.	April 2020
CLIN1	3	1.5	CLIN3 approval go/no-go: Three (3) Master Service Agreements Drafts	Minimum of five (5) Master Service Agreements Drafts shared with our key vendors for negotiation	Master Service Agreements DRAFTs available and shared with at least 3 key vendors for negotiation	April 2020
CLIN1	3	1.5.1	CLIN3 approval go/no-go: Quality Agreement DRAFT	Quality Agreement DRAFT with the System SeptiScan System Contract Manufacturer for negotiation	Quality Agreement DRAFT available and shared with the System SeptiScan System Contract Manufacturer to initiate negotiation	April 2020
CLIN1	1,2,3	1.2.1, 1.2.2, 1.2.3, 1.3.1, 1.4.1	Development Stage Gate Review	Cytovale approved Development Stage Gate records (*e.g. review meeting minutes with any relevant accompanying review materials*) documenting Design Freeze, close of Development and readiness to enter the Verification and Validation stages	Cytovale Engineering and Quality approval of Development Stage Gate demonstrating readiness to enter the Verification and Validation stages	Aug 2020
CLIN1	4	1.2.4	Verification and Validation Plans	Released Verification and Validation Plans for the SeptiScan System, modules (for hardware and software) and consumables: • Master Design V&V plan • System V&V plan • Modules V&V Plan(s) • Consumables V&V Plan(s)	Cytovale approved Verification and Validation Plans are released to Cytovale's QMS	Mar-Aug 2020

Contract Period	AIM#	WBS	Milestone	Deliverable	Success Criteria	Est. Completion Date
CLIN1	4	1.2.4, 1.3.2	Repeatability and Reproducibility Protocols	• Repeatability and Within Lab Precision Study protocol • Lot-to-lot Reproducibility Study of SeptiScan Cartridges protocol	Cytovale and BARDA approved Repeatability and Reproducibility protocols and released to Cytovale's QMS	Apr 2020
CLIN1	4	1.2.4, 1.3.2	Stability Testing Protocol(s)	• Patient sample stability testing protocol • Reagents and cartridges stability testing protocols	Cytovale and BARDA approved Stability Testing protocol(s) and released to Cytovale's QMS	Apr 2020
CLIN1	4	1.4.2	Healthy Reference Range Study Protocol	Healthy Reference Range Study protocol	Cytovale and BARDA approved Healthy Reference Range Study protocol and released to Cytovale's QMS	Apr 2020
CLIN1	4	1.4.2	Clinical Validation Study Protocol	Clinical Validation Study protocol	Cytovale and BARDA approved Clinical Validation Study protocol and released to Cytovale's QMS	Apr 2020
CLIN1	4	1.4.2	CLIN2 approval go/no-go: Analytical Validation, and Clinical Validation Study IRB Approval	One (1) IRB approval received for the following study protocols and template ICF: • Analytical Validation clinical protocol • Clinical Validation Study protocol •	One (1) IRB approval received for the following study protocols and template ICF: • Analytical Validation clinical protocol • Clinical Validation Study protocol •	Apr 2020
CLIN2	12	2.3.1	Clinical Pilot Study #2 (Respiratory Cohort) Study Report	Clinical Pilot Study #2 (Respiratory Cohort) Study Report		July 2020
CLIN2	12	2.2.1 2.2.2 2.3.1 2.4.1	Technical Review(s) records	Cytovale approved Technical Review(s) records (e.g. review meeting minutes with any relevant accompanying review materials) documenting the performance of the SeptiScan System and	Engineering and Quality approved Technical Review(s) records	Apr-Aug 2020

Contract Period	AIM#	WBS	Milestone	Deliverable	Success Criteria	Est. Completion Date
				consumables from pilot engineering pre-verification, analytical performance and clinical pre-validation studies ahead of design freeze		
CLIN2	12	2.3.2, 2.4.2	Clinical Readiness Review	Cytovale approved Clinical Readiness Review Meeting records (*e.g. minutes with any relevant accompanying review materials*), demonstrating clinical operational readiness and capturing approval to enroll for Analytical and Clinical Validation studies	Cytovale Engineering, Clinical Operations, and Quality approval to enroll for Analytical and Clinical Validation Studies	Aug 2020
CLIN2	5	2.4.2 2.4.3	Records of the First Patient In (FPI) enrolled for evaluation in the Analytical Validation Studies	Records of the First Patient In (FPI) enrolled for evaluation in the Analytical Validation Studies, including clinical enrollment record and SeptiScan test result	First Patient In (FPI) enrolled and patient sample successfully processed on the SeptiScan System to provide a SeptiScan Score result.	Aug 2020
CLIN2	5	2.4.2, 2.5.2	CLIN5 approval go/no-go: Shipments of study materials completed	Shipping and inventory records for the study materials shipment to clinical & lab site(s) demonstrating that all study materials shipments have been completed.	All sites have been supplied with needed study materials to complete studies execution (last inventory shipment is completed)	Oct-Nov 2020
CLIN2	5	2.2.5, 2.3.3, 2.4.3	CLIN4 approval go/no-go: Three (3) Completed DRAFT Analytical Validation Reports	DRAFT Analytical Validation Reports: • Patient Sample Stability report • Cartridge lot to lot reproducibility report • Carry over report	Three (3) analytical studies execution and analysis completed, and results summarized into final DRAFT reports available for review: • Patient Sample Stability Study • Cartridge Lot to Lot Reproducibility Study, • Sample Carryover Study	Nov 2020 - Jan 2021
CLIN2	5	2.2.5, 2.3.3, 2.4.3	Final Analytical Validation Reports	Analytical Validation Reports: • Patient Sample Stability report • 3 sites repeatability	Cytovale approved Analytical Validation reports and released to Cytovale's QMS	Dec 2020 - Mar 2021

Contract Period	AIM#	WBS	Milestone	Deliverable	Success Criteria	Est. Completion Date
				study report • Cartridge lot to lot reproducibility report • Carry over report • On-board reagent stability report • Interfering substances report		
CLIN2	5	2.2.5, 2.3.3	Interim Long-Term Stability Report(s)	• Cartridge Interim Long-Term Stability Report • Reagents Interim Long-Term Stability Report(s)	Cytovale approved Interim Long-Term Stability report(s) and released to Cytovale's QMS	Feb-Mar 2021
CLIN2	6	2.3.3, 2.4.3	CLIN4 approval go/no-go: Healthy Reference Range Study Report	Healthy Reference Range Study Report	Cytovale approved Healthy Reference SeptiScan Score Range determined and report released to Cytovale's QMS	Nov 2020 – Jan 2021
CLIN2	7	2.3.3, 2.4.3	Clinical Validation Final Analysis for 510(k) filing	Cytovale approved Clinical Validation final analysis tables and figures ready for 510(k) filing	Approved formatted tables and figures from Clinical Validation final analysis ready for 510(k) filing	Feb-Mar 2021
CLIN2	8	2.6.2, 2.6.3, 2.6.4	CLIN4 approval go/no-go: Regulatory 510(k) submission Interim Review	Cytovale approved 510(k) Submission Interim Review records (*e.g. meeting minutes with any relevant accompanying review materials*) documenting progress of submission package and availability of a subset of completed DRAFT package sections for early review	Cytovale Regulatory approval of Interim Review meeting minutes and availability of a subset of completed DRAFT package sections for early review	Nov 2020-Jan 2021
CLIN3	9	3.2.1, 3.2.2, 3.3.3	CLIN5 approval go/no-go: Supply Chain Interim review	Cytovale approved Supply Chain Interim Review meeting records (*e.g. minutes with any relevant accompanying review materials*) documenting manufacturing scale up and validation planning status ahead of completing Design Transfer	Cytovale Engineering, Operations, and Quality Approval of Supply Chain Interim Review Meeting demonstrating manufacturing scale up and validation planning is on track ahead of completing Design Transfer by end of 2020 / Q1 of 2021.	Oct-Nov 2020

Contract Period	AIM#	WBS	Milestone	Deliverable	Success Criteria	Est. Completion Date
CLIN3	9	3.1.1	CLIN5 approval go/no-go: Launch Plan and Forecast	Cytovale approved Launch Plan and Forecast	Delivery of Launch plan and Year 1-3 revised forecast	Oct-Nov 2020
CLIN4	10	4.6.2	SeptiScan System 510(k) Pre-market notification package	Complete SeptiScan System 510(k) Pre-market notification package as submitted to FDA	510(k) package submitted & administrative acceptance letter from FDA received	Mar-Jun 2021
CLIN4	10	4.2.1, 4.6.1, 4.6.3	510(k) Clearance	510(k) Clearance letter from the FDA for the SeptiScan System	FDA clearance letter received	Oct-Dec 2021
CLIN5	11	5.2.3, 5.5.1, 5.5.2	Manufacturing Transfer Technical Review Records	Cytovale approved Manufacturing Transfer Technical Review records (*e.g. review minutes with any relevant accompanying review materials*) documenting the readiness of the SeptiScan System and consumables to move to production.	SeptiScan System and consumables to move to production approval by Engineering, Manufacturing Operations and Quality.	Mar-Jun 2021
CLIN5	11	5.2.1, 5.7.2	Supply and Quality Agreements	Supply Agreements and Quality Agreements with critical qualified vendors.	Executed supply and quality agreements	Jul-Oct 2021
CLIN5	11	5.2.2, 5.2.3, 5.5.2,	Launch Readiness Review Records	Cytovale approved Launch Readiness Review records (*e.g. meeting minutes with any relevant accompanying review materials*) demonstrating the SeptiScan System is approved for launch.	SeptiScan System is approved for commercial launch.	Oct-Dec 2021

5) Amend CLIN 0002 Go/No-Go Milestone Decision table to show as follows:

CLIN	Go/No-Go Decision Gate Milestone	Success Criteria	Failure Criteria	Go/No-Go Decision Gate Milestone Date	Trigger for CLIN/ Option
CLIN1 *(AIM 3)*	Three (3) QA-Released SeptiScan Systems	Delivery of three (3) SeptiScan Systems with associated documentation to Cytovale	Fewer than 3 Pilot SeptiScan Systems delivered to Cytovale	April 2020	CLIN2
CLIN1 *(AIM 3)*	Two (2) QA-Released	Quality Assurance release of two (2) lots of reagents consumables to inventory with	Fewer than 2 Pilot lots of reagents consumables released to inventory by	April 2020	CLIN2

	Consumables Lots	associated documentation.	Cytovale QA		
CLIN1 *(AIM 4)*	Analytical Validation and Clinical Validation Study) protocols IRB approvals.	One (1) IRB approval received for the following study protocols and template ICF: • Analytical Validation clinical protocol • Clinical Validation Study protocol	No IRB and ICF approval received for any of the study protocols	April 2020	CLIN2