Protocol No.: GenePOC-GBS_clinical-01

Prospective Multi-Center Study for Clinical Validation of the Molecular-Based GenePOC GBS test for the Detection of the *cfb* Gene from *Streptococcus agalactiae* strains in vaginal/rectal swab amples, after Lim Broth enrichment, from antepartum pregnant women.

Protocol version	Version date
Final version (1.0)	2015-Oct-06
1.1	2015-Oct-20
1.2	2015-Nov-02
1.3	2016-Jul-20
1.4	2017-Jan-05

FOR INVESTIGATOR USE ONLY

The performance characteristics of the GenePOC™ GBS system have not been established. To be used by qualified investigators only. The GenePOC GBS system must not be used as a diagnostic procedure without confirmation of the diagnosis by another medically established diagnostic product or procedure.

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REVISION SUMMARY

This revision summary is intended as an aid in understanding the changes being implemented. Review of the summary alone does not ensure complete understanding. The actual text must be reviewed to ensure full understanding of the change(s).

Version	Date	Change(s) description	Section	Reason for change (s)	CRF versions to be used
Final (1.0)	2015-Oct-06	Original	NA	NA	1.0
1.1 (final with minor changes)	2015-Oct-20	Page 3: DELETED: If the change is a protocol amendment, IEC approval is required	REVISION SUMMARY	REASON: as detailed in section 6.6.2.1, approval will be required only if requested by IEC.	1.0
		Page 18 and page 22: Changes in storage temperature for specimens	5.3.1, 6.1 and 6.2	REASON: typewriting error in final version 1.0 and to standardize, throughout protocol, storage temperature requirements	
		Page 27, 28, 32, 33, 35 and 37: Changes in wording of IEC requirements	6.6.2.1, 6.6.3, 8.4, 9.1, 9.7.1 and 11.1	REASON: To request approval from IEC only if needed.	
1.2	2015-Nov-02	Page 20 DELETED: The Study Subject Log will allow reconciliation with the subject's hospital files, if needed.	5.5.1	REASON: Hospital files cannot be accessed if informed consent is not obtained from subject.	1.0
		Page 7 DELETED: but some demographic data will be gathered.	Protocol Summary		
1.3	**2016-Jul-18**	**FONT CHANGED:** cfb put in italics	**Whole document**	**GenePOC nomenclature**	**1.0**
		CHANGED: - GenePOC System **changed for** → GenePOC system - GenePOC GBS Assay **changed for** → GenePOC GBS test - GenePOC **changed for** →GenePOC Inc. - Training manual **changed for** → Study Site Manual - Specimen **changed for** → Sample			
		DELETED: 1.3 Clinical	**1 Sponsor**	**New Information**	

Version	Date	Change(s) description	Section	Reason for change (s)	CRF versions to be used
		Research Associate Section.	**Contact**		
		CHANGED: intended use text modified to match the official intended use	**Protocol Summary and 3.2 Intended Use**	**New information**	
		ADDED: DTT: Disposable Transfer Tool	**2.1 Acronyms**	**GenePOC nomenclature**	
		CHANGED: - GenePOC System Investigation Documents User's Manual changed for →GenePOC instrument User's manual	**2.2 Definitions**	**To match GenePOC documents nomenclature**	
		CHANGED: Disposable Transfer Pipette **changed for** → Disposable Transfer Tool	**3.3 Device Description**	**GenePOC nomenclature**	
		CHANGED: […] must repeat the training panel in duplicate and will be qualified if he/she meets the acceptance criteria for each of the repeated runs independently. changed for (a maximum of two times) **changed for** → […] must repeat the training panel (a maximum of two times) and will be qualified if he/she meets the acceptance criteria for the repeated runs. changed for (a maximum of two times)	**5.2.1 Proficiency Testing**	**Training method updated**	
		CHANGED: […] true negative and high negatives samples. **Changed for → and negative sample**	**5.2.4 second paragraph**	**Not required**	
		DELETED GenePOC GBS in the following sentence**:** Once per day GenePOC GBS, a reference GBS […].	**5.2.4 Last paragraph**	**Typo error**	
		CHANGED: The operator will save the instrument data on two(2) properly labeled USB keys on each testing day. Once or twice per week, one USB key must be sent to GenPOC. The other USB key must be maintained as a backup at the	**5.5.2 GenePOC Data and appendix A**	**New information**	

Version	Date	Change(s) description	Section	Reason for change (s)	CRF versions to be used
		Clinical Center. **Changed for →** The operator will save the instrument data on properly labeled USB keys on each testing day. On every testing day, data will be uploaded to study specific database			
		CHANGED in 2nd bullet:- VWR Multi Tube Vortexer (VWR catalog no. 58816115) and appropriate vial holder; **changed for →** Tube Vortexer **ADDED to 4th bullet:** (including PIE, SBT and DTT) **DELETED from 8th bullet:** isolates **DELETED from 10th bullet:** Required calibrated pipettes **DELETED from 11th bullet:** broths and isolates **DELETED from 12th bullet:** "and shipping to GenePOC once or twice per week" **CHANGED in 13th bullet:** microfluidic cartridges **changed for → PIE**	**5.6.1 Provided by GenePOC**	**Administrative changes**	
		ADDED to 2nd bullet: GBS collection (if available)	**5.6.2 Provided by Investigator**	**Due to multiple collection sites, GBS sampling procedures may not be available**	
		DELETED: The vaginal/rectal swab should be placed into its designed transport media (Amies or Stuart). Care should be taken not to mix stool, water, urine or soap in the sample" **ADDED:** Vaginal/Rectal swab should be performed in accordance with published guidelines for collection of clinical specimens for culture of Group B Streptococcus (CDC in United States and SOGC in Canada).	**6.1 Sample Collection**	**To reflect what is done in this study using left over sample**	
		DELETED: Fresh specimens stored at 2-25°C can be tested with the GenePOC	**5.3.1 Inclusion Criteria and**	**New information**	

Version	Date	Change(s) description	Section	Reason for change (s)	CRF versions to be used
		GBS System and the Reference Method up to 96h of collection. **ADDED:** If the sample will be processed within 24 hours, store at room temperature. If the sample will be tested after 24 hours, refrigerate until testing is performed. Sample stored at 2-8°C can be tested with the GenePOC GBS System and the Reference Method up to 96h of collection.	**6.2 Sample Storage and Handling,** 3rd Bullet		
		CHANGED: External control materials are not provided by GenePOC. Commercially available control material may be used or a ≥18 hour GBS culture in Lim Broth may be utilized as positive control material. GBS (*Streptococcus agalactiae* ATCC 12973) is a recommended strain to use as a control. An uninoculated GBS Sample Preparation Reagent tube or a 15 µL aliquot of pure Lim Broth is recommended for use as an external negative control. Preparation of these controls will be detailed in the Package Insert and in the Training Manual. **Changed for →** External control materials are provided by GenePOC. A reference GBS strain bearing the *cfb* gene (e.g. ATCC 12973) will be used as a positive external control (EC) while not inoculated Lim broth will be used as a negative EC.	**6.5.1.1 External Controls and 6.5.2 Reference Method**	**New Information**	
		CHANGED: Broth enrichment culture Plate (15 µL) **changed for →** (100-150 µL)	**Appendix B**	**Typo error**	
1.4	**2017-Jan-05**	CHANGED: Rachelle Nadeau, B.Sc. for	**Whole document**	**New Study Manager**	

Version	Date	Change(s) description	Section	Reason for change (s)	CRF versions to be used
		Catherine Lippé, M.Sc. and contact information was modified			
		DELETED: The GenePOC GBS System and the Reference Method not performed according to the GenePOC GBS Investigation Documents	**Exclusion criteria**	**This sentence was written twice**	
		ADDED: When it is confirmed that no repeat on fresh Lim broth culture is necessary, it will be transferred to a single appropriately labelled tube and frozen at -70±5°C or colder for further testing of all negative frozen samples and /or possible future discrepant testing.	**6.3 Testing algorithm**	**New Information**	
		ADDED: 6.3.2.3. Repeat of negative samples for the Reference Method In case of suspected irregularity in the testing of the reference method, the entirety of the specimens that gave a negative result with the reference method could be re-tested at a single testing site according to section 6.3.2. In this case, the tested material will be the frozen LIM broth culture stored at -70^{0}C.	**6.3.2 Reference Method**	**New Information**	

PROTOCOL ACCEPTABILITY

Protocol Proposed by:

_____ _____

Catherine Lippé M.Sc
Study Manager
GenePOC inc.

Date (yyyy-mmm-dd)

Acceptability

I have reviewed and understood this protocol and agree to its provisions. Any modifications must be made by written mutual agreement.

Clinical Center

Address: _____
_____
_____
_____

_____
Principal Investigator Name

_____ _____

Principal Investigator Signature

Date (yyyy-mmm-dd)

Sponsor

_____ _____

Dany Leblanc, Eng
Director QA/RA
GenePOC Inc.

Date (yyyy-mmm-dd)

PROTOCOL SUMMARY

Study Protocol Number	**GenePOC-GBS_clinical-01**
Protocol Title	Prospective Multi-Center Study for Clinical Validation of the Molecular-Based GenePOC™ GBS test for the Detection of the *cfb* gene from *Streptococcus agalactiae* strains in vaginal/rectal swab sample, after Lim Broth enrichment, from antepartum pregnant women.
System Summary	The primary purpose of this clinical investigation is to verify the performance of the GenePOC GBS test on the GenePOC system. This will be achieved by comparing the GBS test to the Culture, a conventional method for detection of *Streptococcus agalactiae* in vaginal/rectal swab samples.
Study Locations	Up to four (4) geographically diverse Canadian (2) and US (2) Clinical Centers are targeted, with each site testing high volumes of samples for GBS combined with high prevalence rates and ability to perform the reference method.
Intended Use	The GenePOC GBS test performed on the GenePOC system is a qualitative in vitro diagnostic test designed to detect Group B Streptococcus (GBS) DNA from vaginal/rectal swabs from antepartum women following enrichment in Lim broth for 18-24 hours. The GenePOC GBS test utilizes automated sample preparation and real-time polymerase chain reaction (PCR) to detect a *cfb* gene sequence specific to the *Streptococcus agalactiae* genome. The GenePOC GBS test is indicated for the identification of antepartum GBS colonization and does not provide susceptibility results. Culture isolates are needed for performing susceptibility testing as recommended for penicillin-allergic women.
Investigational Product (IUO)	The GenePOC GBS test will be performed according to the Study Protocol using the GenePOC™ instrument. The GenePOC system, used in conjunction with appropriate reagents, is capable of automated cell lysis, dilution of nucleic acids from multiple sample types as well as automated amplification and detection of target nucleic acid sequences.

Reference Method	Culture is defined as Lim broth culture, subcultured onto blood agar plate (BAP) for observation of a *Streptococcus agalactiae* strain. More specifically, the *Streptococcus agalactiae* bacteria, when present, will be isolated using an Enriched Culture and then identified by usual microbiological method. The exact same media type, reagents and procedure will be used for performing the Reference Method throughout the clinical investigation by all sites.

Phase	Development Phase - Qualification of investigational device (IUO).
Planned Study Period	Clinical investigation to begin in January 2016 at the earliest and to be completed within approximately 8 weeks.
Planned Sample Size	The purpose of the clinical investigation is to enroll sufficient samples from four (4) Clinical Centers to obtain a total of 150 samples positive for GBS based on the Reference Method final result. With an estimated prevalence of approximately 25%, up to 600 samples will be tested across all Clinical Centers. The performance obtained and the confidence interval will be monitored during the study in order to stop the enrollment when appropriate. A minimum of 30 positive results per site is expected but sites with a higher prevalence of GBS could contribute with more positive results to reach the required number.
Objectives	The primary objectives of this multi-center prospective investigational trial are: • To establish the performance characteristics of the GenePOC GBS Assay for its use to detect Group B Streptococcus (GBS) DNA from Lim broth cultures. Sensitivity and specificity will be established in comparison to the Reference Method. • To estimate the Positive and Negative Predictive Values (PPV and NPV) of the GenePOC GBS Assay. • To estimate the rate of unresolved results for the GenePOC GBS Assay due to Sample Processing Control failure (Unresolved sample results). • To estimate the rate of indeterminate results for the GenePOC GBS Assay due to an Instrument failure (Indeterminate sample results). • To determine the reproducibility between sites of the GenePOC GBS System.

Study Design	Four (4) geographically diverse Clinical Centers will be selected based on a number of criteria, such as investigator and site personnel availability, number of samples of interest tested for *Streptococcus agalactiae,* GBS prevalence, familiarity with the Study Reference Method, experience with *Streptococcus agalactiae* culture isolation and clinical studies. Site(s) that will perform the Reference Method will have laboratory facilities where *Streptococcus agalactiae* characterization methods are performed for routine, investigation or research purposes. This clinical investigation will be composed of the following segments: Proficiency testing, Clinical Accuracy, Discrepant testing (optional) and Assay Reproducibility (selected sites). There are no risks to the patient inherent to the execution of this investigation since it will: 1) Be performed on excess de-identified samples only; *and* 2) Include parallel clinical routine testing by an approved and established method for reporting patient results. Results obtained from testing using the GenePOC GBS System will be compared to those obtained by the Reference Method. Investigators will ensure that, for a given sample, the participating technicians performing the Assay are masked from the results of the Reference Method and vice-versa. Electronic and/or paper Case Report Form(s) will be used to record pertinent sample and laboratory information. No personal subject information will be collected by GenePOC. In cases of discrepant results between the Reference Method and the GenePOC GBS Assay, GenePOC staff will perform further characterization testing to elucidate the discrepancies.

Clinical Study Main Eligibility Criteria	• Antepartum pregnant women • 18 years old and more • Gestation period at 35 to 37 weeks • Only one (1) sample per patient will be included in the study. • If the sample will be processed within 24 hours, store at room temperature. If the samples will be tested after 24 hours, refrigerate until testing is performed. Samples stored at 2-8°C can be tested with the GenePOC GBS System and the Reference Method up to 96h of collection.
Clinical Study Statistical Methods	Results obtained with the GenePOC GBS System will be compared to those obtained with the Reference Method. The statistical analyses will include all compliant samples and will determine at least the following: • The sensitivity and specificity, PPV and NPV as well as exact 95% confidence interval. • The unresolved and indeterminate rates along with 95% exact confidence interval. • Poolability of the data. • Reproducibility percent agreements for qualitative and quantitative data.

TABLE OF CONTENTS

1. SPONSOR CONTACTS

1.1. Sponsor

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2. TERMINOLOGY

2.1. Acronyms

BAP	Blood Agar Plate
bp	Base pairs
CDA	Confidentiality Disclosure Agreement
CDC	Centers for Disease Control and Prevention
CLIA	Clinical Laboratory Improvement Amendments
CRA	Clinical research associate
CTA	Clinical Trial Agreement
DNA	Deoxyribonucleic Acid
DTT	Disposable Transfer Tool
EC	External control
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
GBS	Group B Streptococcus
IEC	Independent Ethics Committee
INC	Inconclusive
IND	Indeterminate
IRB	Investigational Review Board
IUO	Investigational use only
NPV	Negative predicative value
PC	Process Control
PCR	Polymerase Chain Reaction
PI	Principal investigator
PPV	Positive predictive value
SB	Sample Buffer
SBT	Sample Buffer Tube
UNR	Unresolved

2.2. Definitions

Clinical Center(s)	The site(s) that will perform the GENEPOC GBS test and, the culture method for the clinical study.
GENEPOC GBS	Documents provided to investigators by GenePOC including the GenePOC instrument User's Manual, the GenePOC GBS Study Protocol, the GenePOC GBS Package Insert and the GenePOC GBS Study Site Manual.
GENEPOC GBS System	The system is composed of the GenePOC GBS test which is used in conjunction with the GenePOC™ instrument.
PCR Operator	Participating laboratory technician who has successfully completed the proficiency testing
PIE	GBS disposable microfluidic cartridges (describe in this document as PIE because of the shape of the cartridge).
Principal Investigator	Principal Investigator (PI): A person who actually conducts the clinical investigation, under whose immediate direction the test article (device) is used involving a sample derived from a human subject; or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team.
Reference Method	The Reference Method for this study will be the Culture, a culture method to detect *Streptococcus agalactiae* strain from a sample.
Sample	Left over Lim broth enrichment intended for regular culture.
Sponsor	GenePOC Inc.
(Patient) sample	Vaginal/rectal swab samples collected for routine laboratory testing from a pregnant woman suspected to be colonized with *Streptococcus agalactiae* (GBS).

3. INTRODUCTION

3.1. Protocol Scope

The purpose of this clinical investigation is to establish the performance characteristics of the GenePOC GBS system for its use in determining the presence of GBS in vaginal/rectal swab samples, after Lim Broth enrichment, from pregnant women. Sensitivity and Specificity will be established in comparison to the Reference Method. For this investigation the Reference Method will be Lim broth culture, subcultured onto blood agar plate (BAP), routine method for detection of GBS coming from vaginal/rectal swab samples. Up to four (4) selected sites will perform this clinical investigation.

3.2. Intended Use

The GenePOC GBS test performed on the GenePOC System is a qualitative in vitro diagnostic test designed to detect Group B Streptococcus (GBS) DNA from vaginal/rectal swabs from antepartum women following enrichment in Lim broth for 18-24 hours. The GenePOC GBS test utilizes automated sample preparation and real-time polymerase chain reaction (PCR) to detect a *cfb* gene sequence specific to the *Streptococcus agalactiae* genome. The GenePOC GBS test is indicated for the identification of antepartum GBS colonization and does not provide susceptibility results. Culture isolates are needed for performing susceptibility testing as recommended for penicillin-allergic women.

3.3. Device Description

The GenePOC GBS test will be performed using the GenePOC instrument. The GenePOC instrument, used in conjunction with appropriate reagents, is capable of automated lysis cells, dilution of nucleic acids from multiple sample types as well as automated amplification and detection of target nucleic acid sequences.

The GenePOC GBS Assay reagents kits consist of:

Components	Packaging
Sample Buffer Tube (SBT)	A 4.5ml tube containing 1ml of sample buffer
Disposable Transfer Tool	Plastic disposable transfer pipette for transferring inoculated sample buffer (SB) into the PIE.
GBS disposable microfluidic cartridges (PIE)	Fully integrated disposable microfluidic cartridge for detection of GBS.

3.4. Test Principle

The study population consists of vaginal/rectal swab samples from pregnant women at 35-37 weeks of gestation for whom GBS diagnostic procedures are indicated and ordered. After the sample is collected and transferred into the transport media (Amies or Stuart), it is transported to the laboratory and stored at the appropriate temperature for no more than 96 hours.

When ready for testing, the swab is placed into a culture tube with Lim Broth for 18-24 hours. After incubation, a 15 µL aliquot of the broth is used for detection of the presence of GBS. The aliquot of the broth is mixed with GenePOC Sample Buffer Tube Reagent (SBT) and then vortex for 5 seconds, 100 to 200 µL of the Sample-SBT mix is transferred to the GBS PIE using the disposable transfer pipette. GBS PIE is then transferred into the GenePOC System for fully integrated real time analysis.

The GenePOC GBS test includes reagents for the simultaneous detection of the target GBS DNA, a process control (PC) to monitor processing, amplification, and the absence of reaction inhibitors. The GBS primers and probe detect a target region of 190 base pairs (bp) of the *cfb* gene of *Streptococcus agalactiae*. The results are interpolated by the system from measured fluorescent signals and embedded calculation algorithms. Results may be viewed, be printed, transferred and/or stored by the user.

3.5. Clinical Benefits and Justification for the Use of a New Technology

The group B streptococcus (*Streptococcus agalactiae*, GBS) is a cocci gram-positive bacterium that is one of the main causes of neonatal mortality in developed countries. Neonatal infections caused by GBS are found in two forms[1,2], early or late onset. The early-onset infections occur during the 7 days following birth; they are the cause of approximately 80% of GBS infections in newborns with mortality rate of 5-20%[3]. The late onset infections occur between the first week and the seventh month of life. They are rarer and the mortality rate is lower. In the case of early-onset infections, GBS is transmitted during childbirth via the genital tract of the mother while for late onset infections, contamination is not necessarily via the mother[4]. Prolonged hospitalization and the use of expensive equipment is generally required for GBS infected newborn care. Survivors may also suffer permanent damage such as mental developmental delay or loss of vision.

Currently, the clinical guidelines of the Centers for Disease Control and Prevention[5] and the Canadian Society of Obstetricians and Gynaecologists[6] recommend the use of a GBS screening during pregnancy (antepartum) combined with a treatment of antibiotics for prophylaxis during delivery (intrapartum) to all women detected GBS positive. This approach has reduced the incidence of perinatal GBS infections in North America[7]. Unfortunately, the presence of a vaginal colonization in pregnancy does not necessarily indicate the presence of a settlement at the time of delivery. Some women are treated when they are no longer carriers of GBS, while others are not, consequently they will be carrying GBS at the time of delivery.

A first version of a screening test by polymerase chain reaction (PCR) in the early 2000s has demonstrated the usefulness of a rapid detection of GBS[8]. This method however, was not fully integrated (independent lysis method of PCR system), unlike the GenePOC system, limiting its use to hospital laboratories.

The GenePOC GBS test is a step further in rapid detection of GBS by increasing the automation of the detection and simultaneously increasing the ease-of-use.

4. TRIAL OBJECTIVES

The objectives of this multi-center prospective clinical study are:

- To establish the performance characteristics of the GenePOC GBS System for its use in determining the presence of GBS in vaginal/rectal swab, after Lim Broth enrichment, samples from antepartum pregnant women. Sensitivity and specificity will be established in comparison to the Reference Method.
- To estimate the Positive and Negative Predictive Values (PPV and NPV) of the GenePOC GBS System.
- To estimate the rate of unresolved results for the GenePOC GBS System due to Sample Processing Control failure (Unresolved sample results).
- To estimate the rate of indeterminate results for the GenePOC GBS test due to an Instrument failure (Indeterminate sample results).
- To determine the reproducibility between sites of the GenePOC GBS System.

5. STUDY DESIGN

5.1. Clinical Investigation Requirements

Up to four (4) GenePOC GBS clinical centers will participate in the clinical study. Clinical centers will be selected for the clinical study based on a number of criteria, such as investigator and site personnel availability, number of samples of interest tested for GBS, GBS prevalence, familiarity with the study Reference Method, and experience with GBS culture isolation and clinical investigations.

Site(s) will have a laboratory where GBS characterization methods are performed for routine, investigation or research purposes. The exact same media type, reagents and procedure will be used for performing the Reference Method throughout the clinical investigation by all sites.

The Clinical investigation requirements relating to each Clinical Centers are detailed in Appendix A.

5.2. Overview of the Evaluation

The Clinical investigation will consist of four (4) distinct segments: Proficiency testing, Clinical Accuracy testing, Discrepant testing (optional) and Assay Reproducibility (selected sites).

5.2.1. Proficiency Testing

Each PCR operator who will participate in the GenePOC GBS clinical study will be trained by a GenePOC Study Manager (or CRA) on handling and performing the GenePOC GBS testaccording to the Investigational Use Only (IUO) Package insert, the Study Site Manual and the GenePOC System User's Manual.

A test panel containing negative samples and GBS positive samples will be used to assess each new participating technician proficiency with the protocol test methods. This panel will be provided in a sufficient number and will contain negative samples and GBS positive samples. A participating technician failing to achieve the qualification criteria on initial testing of the GenePOC GBS System must repeat the training panel (a maximum of two times), and will be qualified if he/she meets the acceptance criteria for the repeated runs. If the participating technician fails to meet the retest criteria, he/she cannot be qualified for participation in the GenePOC GBS clinical study as a PCR operator for the GenePOC GBS System unless re-training occurs and the participating technician is able to pass the proficiency test.

To be qualified for participation in the GenePOC GBS clinical study as a PCR operator, each participating technician must achieve a correct answer for all positive samples and true negative (no target) samples in the molecular method using the provided proficiency panel.

For the Reference Method no proficiency testing will be done.

If a new participating technician is included in the study after the initial training and proficiency testing occurs, the training of this person can be performed by a GenePOC representative or by a proficient PCR operator on-site. The new participating technician must also pass the proficiency test to participate in the study.

5.2.2. Clinical Accuracy Testing

This clinical study is designed in such a way that all sites may perform the Reference Method, which requires that each Clinical Center has laboratory facilities where GBS characterization methods are performed for routine, investigation or research purposes. Reference method is defined as Lim broth culture, subcultured onto blood agar plate (BAP) for detection of *Streptococcus agalactiae* strains. More specifically, the *Streptococcus agalactiae* bacteria, when present, will be isolated using an Enriched Culture method. The exact same media type, reagents and procedure will be used for performing the Reference Method throughout the clinical investigation by all sites.

To be considered for enrollment in the study, a sample must satisfy all eligibility criteria

described in Section 5.3 of this Protocol. Samples will be collected using a swab.

Sample testing will be performed according to Section 6 of this protocol. Results obtained from testing of samples using the GenePOC GBS System will be compared to those obtained by the Reference Method. These results will serve to verify the GenePOC GBS System performance.

GenePOC GBS System and Reference Method testing will be performed as described in the GenePOC GBS Investigation Documents and the testing algorithm shown in Appendix B. Investigators will ensure that, for a given sample, the PCR operator performing the test are masked from the results of the Reference Method and vice-versa.

The purpose of the clinical investigation is to enroll sufficient samples to obtain approximately 150 positives samples for GBS based on the Reference Method final result. With an estimated prevalence of approximately 25%, it is projected that up to 600 samples will be needed across all participating Clinical Centers.

The Study Manager will monitor sample enrollment and prevalence of GBS across all participating Clinical Centers. It may be necessary to increase the enrollment rate of samples or to prematurely stop enrollment at one or more participating centers, depending upon the total number of samples and the positive samples obtained across all Clinical Centers.

At least three (3) lots of the GenePOC GBS Assay kits will be used for this Clinical trial. Each Clinical Center with test a minimum of two (2) lots.

Once per day, a reference GBS strain bearing the *cfb* gene (e.g. American Type Culture Collection, ATCC 12973) will be used as a positive external control (EC) while not inoculated sample buffer will be used as a negative EC. If either or both of the ECs fail to give the expected result, all samples tested in that run will be repeated from the remaining SBT containing the sample stored at 2-8°C along with new positive and negative ECs.

5.2.3. Discrepant Testing *(optional)*

In cases of discrepant results between the Reference Method and the GenePOC GBS Assay, further characterization testing may be requested by GenePOC to be performed by the Clinical Center and possibly at GenePOC to attempt to resolve the discrepancy. See Section 6.3.3 and Appendix C for description of the minimal discrepant testing. An electronic or paper Discrepant Results Form will be used for recording discrepant testing information.

5.2.4. Assay Reproducibility Testing *(for selected sites)*

Reproducibility study will be performed with a panel of samples spiked at 4 different concentrations of GBS: Negative, High negative (1/50x LOD), Low positive (1.5x LOD), Moderate positive (3x LOD). Each panel will consist of 8 samples with 2 replicates of each concentration.

The site-to-site reproducibility will test the same reproducibility panel at three (3) designated sites (2 external sites and GenePOC laboratories) for the within-run (3 replicates), between-run (2 runs per day) and between-day (5 days, consecutive or not) variance with multiple operators and instruments. A single lot of the GenePOC GBS test will be tested by each sites according to the Study Site Manual instructions and the IUO GBS test Package Insert.

The reproducibility panel will contain randomized moderate positive, low positive and negative samples.

Once per day, a reference GBS strain bearing the *cfb* gene (e.g. ATCC 12973) will be used as a positive external control (EC) while not inoculated sample buffer will be used as a negative EC. If either or both of the ECs fail to give the expected result, all samples tested in that run will be repeated from the remaining SBT containing the sample stored at 2-8°C along with new positive and negative ECs.

5.3. Study Criteria

Note: For this study, samples will not be collected for the express purposes of this evaluation. Only excess de-identified samples will be used.

5.3.1. Inclusion Criteria

- Antepartum pregnant women
- 18 years old and more
- Being at a gestation period of 35 to 37 weeks.
- Vaginal/rectal swab sample
- Transport and storage times, and conditions (e.g. room temperature and/or refrigerated) within the labeled indications.
    - **:** If the sample will be processed within 24 hours, store at room temperature. If the sample will be tested after 24 hours, refrigerate until testing is performed. Sample stored at 2-8ºC can be tested with the GenePOC GBS System
    - Fresh sample must be tested with the Reference Method within 96 hours (4 days) of collection if kept at 2-25°C
- The GenePOC GBS System and the Reference Method will be performed according to the GenePOC GBS Investigation Documents.
- Materials use within their expiration date

5.3.2. Exclusion Criteria

- Non pregnant women
- Less than 18 years old
- Gestation not between 35-37 weeks
- Transport and storage times and conditions that exceed these Study Protocol requirements
- The GenePOC GBS System and the Reference Method not performed according to the GenePOC GBS Investigation Documents
- Materials used beyond their expiration date
- Samples without all test results required by this Study Protocol. Samples that are inadvertently entered into the study that do not meet the sample inclusion criteria will be made non-compliant.

5.4. Sample Size Justification

The purpose of the clinical investigation is to enroll sufficient samples from up to four (4) Clinical Centers to obtain a minimum of 150 and a maximum of 160 samples positive for GBS based on the Reference Method final result. With an estimated prevalence of approximately 25%, up to 600 samples could be tested across all Clinical Centers.

A minimum of 30 positive results per site is expected but sites with a higher prevalence of GBS could contribute more positive results to reach the required number. A potential minimum of 200 samples and a potential maximum of 300 total samples will be obtained at each clinical center.

The performance obtained and the statistical confidence intervals will be monitored during the study in order to stop the enrollment when deemed appropriate.

5.5. Data Collection

The principal investigator (PI) will ensure that each designee and the scope of the designee's delegated authority are recorded on the Site Signature and Delegation of Authority Log. The designee's signature, initials, start and end dates, list of study related tasks, and document review and approval must be recorded on the form.

5.5.1. Case Report Forms

All Clinical Centers will use electronic data capture (EDC) through an electronic Case Report Forms (eCRF).
An eCRF will be completed for each sample enrolled in the study in order to record relevant demographic, clinical and laboratory information. These forms must be

completed and approved as described in the Study site Manual and as instructed during the training.

Patients whose sample will be included in the study will not be identified by name or by hospital medical record number on the eCRF. A field is available for a study-specific patient identifier code which will uniquely identify each subject. This code will be assigned by a designated individual at the Clinical Center., who is not directly involved in any other aspects of the study. This code will be a series of:

- 5 digit XX-00Y (X being the site number and Y the samples number attributed sequentially
- And three letters FML: (F being the first letter of the First Name; M being the first letter of the Middle Name or a dash (-) if the persons does not have a middle name; L being the first letter of Last name). As per local regulations, initials can also be a series of three letters determined by clinical center.

This code will have no relation with protected health information, and will be used only to track subject enrollment. A Study Subject Log associating each patient with its patient identifier code will be maintained in a secure location on-site by the designated individual assigning the codes to the patients. Neither the investigator, nor any member of the study team will have access to this log.

Each enrolled sample will be assigned a unique Study Number, which will be identified by bar code labels to be provided by GenePOC. Study Numbers will conform to seven (7) characters in a "GXnnnnA" format: where "G" is a letter identifying the assay (GBS), "X" is a letter identifying the site, "nnnn" is an incrementing number identifying each sample within a study segment, and "A" is a letter denoting the study segment, ("A" for Accuracy or "D" for Discrepant testing). For panel members provided by GenePOC for testing, the same study number pattern will be used and the study segment will be identified as follows: "P" for Proficiency, “R” for Reproducibility and "W" for Workflow Practice.

5.5.2. GenePOC Data

The operator will save the instrument data on properly labeled USB keys on each testing day.On every testing day, data will be uploaded to study specific database.

5.6. Study Materials

5.6.1. Provided by GenePOC

- GenePOC starter kit will minimally contain the following components:
  - GenePOC Instrument
  - GenePOC Sample Racks;
  - GenePOC System User's Manual.
- Tube Vortexer
- Instructions and Training Materials for the Study (*Study Site Manual)*;
- GenePOC GBS test IUO kits (including PIE, SBT and DTT);

- CRFs and other required electronic and printed forms;
- Barcode labels with study numbers for all samples and study segments;
- Masked and randomized proficiency panel of characterized samples;
- Shipping materials ice packs, shipping boxes, labels and GenePOC FedEx account number for returning samples, forms, material and equipment, and any other study-required shipping;
- GenePOC Import permit (into Canada) for pathogens (US sites only);
- Freezer boxes, plastic microtubes and screw-caps;
- Sufficient numbers of USB keys for instrument data daily backup;
- Plastic bags to hold/store and ship PIE;
- Swabs for environmental testing;
- Listing for Study binder(s) indicating essential information for archiving purposes at the closing of the study;
- Technical and engineering support as needed;
- Miscellaneous supplies as agreed upon.

5.6.2. Provided by Investigator

- Sample meeting the eligibility criteria outlined in Section 5.3 above;
- Copies of the laboratory's procedures for the GBS collection (if available), routine diagnostic method and quality control;
- Material for routine testing of GBS:
    - Transport media (Amies or Stuart)
    - Lim broth;
    - Blood agar plate (BAP);
    - Tests for identification;
- Facilities, time and personnel necessary to perform the evaluation according to this Study Protocol, and manage the study records according to the Training Manual, the GenePOC instructions and Regulatory Requirements;
- Import permit provided by the CDC (into US only) for pathogens including at least *Streptococcus* genera.
- Trained personnel in the preparation and shipment of biological substances per CDC (USA sites only), Transportation of Dangerous Goods Regulations 14 (TDGR) (Canadian sites only), and IATA guidelines (all sites);
- Incubator at 35-37°C;
- Vaginal/rectal swab;
- All equipment and supplies necessary to perform Reference Method testing, except as noted in previous section;
- Secure room temperature storage space for the GenePOC GBS Assay kits and culture media (as required by package inserts and study Training Manual);
- Adequate refrigerator (between 2°C and 8°C) for the storage of culture media, reference kits (as required by Package Inserts) and fresh samples;

- Adequate storage space in a -70±5ºC freezer or colder to hold frozen SBT, broths, isolates and panels;
- Control organisms for Reference Method and external control, i.e. *Streptococcus agalactiae* strain (e.g. ATCC 12973);
- Dry ice to send frozen SBT and isolates to GenePOC;
- Site policies or procedures to prevent the release of personal information about patients to the investigator;
- Miscellaneous supplies as agreed upon.

6. LABORATORY TESTING PROCEDURES

6.1. Sample Collection

Vaginal/Rectal swab should be performed in accordance with published guidelines for collection of clinical samples for culture of Group B Streptococcus (CDC in United States and SOGC in Canada).
Samples should be transported to the laboratory according to the hospital's policies but viability of GBS is preserved in transport medium for up to 4 days between 2ºC to 25ºC.

6.2. Sample Storage and Handling

- Samples that meet the study criteria should be labelled with a bar coded study number provided by GenePOC;
- All relevant information regarding the sample will be recorded on the eCRF;

If the sample will be processed within 24 hours, store at room temperature. If the sample will be tested after 24 hours, refrigerate until testing is performed. Sample stored at 2-8ºC can be tested with the GenePOC GBS System and the Reference Method up to 96h of collection.

6.3. Testing Algorithm

Results obtained with the GenePOC GBS System will be compared to those obtained with the Reference Method. All Clinical Centers will be using the same protocol, media and the same Reference Method to ensure uniformity of the test methods across sites. The Reference Method is described in detail in Section 6.3.2 of this protocol.

The vaginal/rectal swab sample will follow the normal hospital path up to the Lim Broth culture, of which an aliquot will be transferred to the GenePOC sample buffer tube (SBT) to be processed with the GenePOC instrument as described in the GenePOC GBS test Package insert. Lim Broth culture remaining in the container will then be used to start the Reference Method.

Lim broth culture must be kept at 2-8°C after testing for a maximum of five (5) days.

When it is confirmed that no repeat on fresh Lim broth culture is necessary, it will be transferred to a single appropriately labelled tube and frozen at -70±5°C or colder for further testing of all negative frozen samples and /or possible future discrepant testing.

The SBTs will be placed at 2-8°C in the event repeat testing is required. If the sample does not require repeat testing, the SBT will be frozen at -70±5°C.

6.3.1. GenePOC GBS Assay

The GenePOC GBS Assay will be performed according to the assay Package insert.

6.3.1.1. Non-Reportable Results

Samples that initially produce a non-reportable result (Unresolved, indeterminate or External Control failure) will be repeated as described below. Samples that have a reportable (Positive, Negative) result upon repeat testing will be included in the data analyses. Repeated samples that do not give a reportable result will not be included in data analyses. They will be reported separately as non-reportable samples.

6.3.1.1.1. Unresolved Samples (UNR)

An Unresolved Sample is when the internal control fail (no amplification) and the target reaction (GBS) also show no amplification.

An Unresolved sample will be repeated from the refrigerated SBT. These samples may be repeated alone, with other samples to be repeated, or included in a new run with fresh sample. In cases where the sample is Unresolved again, no additional repeat testing will be performed.

6.3.1.1.2. Indeterminate Result (IND)

For an Indeterminate (IND) result due to an instrument failure, testing of the sample(s) will be repeated from the refrigerated SBT and may be tested with other samples that require repeat testing, or included in a new run with fresh samples. For any IND result, the Study Manager should be contacted and the incident must be documented on the eCRF.

6.3.1.1.3. External control failure

In case of a failure of either or both external control, the testing of all clinical samples and any repeated samples included in the run will be repeated from the refrigerated SBTs along with new external control (see Section 6.5 for details). In cases where external control fails again, the Study Manager should be contacted.

6.3.2. Reference Method

The Group B streptococcus bacteria, when present, will be isolated from vaginal/rectal swab samples from pregnant women using a Lim Broth culture and subcultured on Blood agar plate (Important note, only Lim Broth could be used for the study). The swab will be inoculated into a Lim broth (Todd-Hewitt broth supplemented with colistin (10 µg/ml) and nalidixic acid (15 µg/ml)). Incubate inoculated selective broth for 18–24 hours at 35°–37°C in ambient air or 5% CO_2. Subculture the incubated broth on a non-selective blood agar plate (e.g., tryptic soy agar (TSA) with 5% defibrinated sheep blood). After incubation for 18–24 hours at 35°–37°C in ambient air or 5% CO_2, inspect agar plates and identify organisms suggestive of GBS (e.g., large, gray colonies with narrow zone of beta hemolysis). If GBS is not identified after incubation for 18–24 hours, then plates should be reincubated overnight and examine for suspected GBS colonies.

6.3.2.1. GBS Identification

Colonies morphologically resembling GBS from blood agar plate (large, gray, and translucent with a small zone of beta-hemolysis or no zone of hemolysis) will be confirmed as follows:

- Catalase negative;
- Gram-positive cocci in pairs and chains;
- And one of the following positive reactions:
    - Group B streptococcal grouping antisera;
    - Camp test;
    - Rapid hippurate and:
    - PYR test negative if strain is hemolytic (Enterococci can be haemolytic, hippurate positive but PYR positive) or a second previous test if strain is nonhemolytic.

Note: no chromogenic agars could be used as FDA has not cleared any.

6.3.2.2. Inconclusive Result

For an Inconclusive (INC) result in the Reference Method due to a non-interpretable blood agar plate, sample will be retested from the existing inoculated and incubated Lim broth. The Lim broth kept at 2-8°C should be used to inoculate a new blood agar plates as directed in Section 6.3.2.

6.3.2.3. Repeat of negative samples for the Reference Method

In case of suspected irregularity in the testing of the reference method, the entirety of the specimens that gave a negative result with the reference method could be re-tested at a single testing site according to section 6.3.2. In this case, the tested material will be the frozen LIM broth culture stored at -70ºC.

6.3.3. Discrepant Testing

Frozen Lim Broth and frozen SBT coming from discrepant result samples will be send to GenePOC for further testing.

During the course of the trial, the GenePOC Study Manager will inform the sites which samples require to be ship to GenePOC.

6.4. Storage & Shipping

- SBT samples must be kept at 2-8ºC after testing for a maximum of five (5) days. When it is confirmed that no repeat is necessary, they will be frozen at -70±5ºC or colder for possible future discrepant testing;
- All Lim broths (*Streptococcus agalactiae* isolates) must be stored at -70±5ºC or colder, but only samples requested by the Study Manager must be shipped on dry ice to GenePOC;
- All microfluidic cartridges (containing amplified product) must be stored between 2ºC to 8ºC in a plastic bag and shipped on icepacks to GenePOC as directed by Study Manager.
- Detailed shipping instructions will be provided in the Training Manual.
- At the end of the trial, clinical center will be instructed by Study Manager to destroy, as per their institution policy, samples that did not require shipment to GenePOC.

6.5. Quality Control Testing

In addition to the quality assurance and quality control programs of each laboratory under their respective certification (e.g. CLIA), the minimum quality control described below must be performed during the course of this study.

6.5.1. GENEPOC GBS Assay

6.5.1.1. External Controls

For each day in which samples are processed, appropriate positive and negative external control (ECs) will be tested. These external controls results will need to be kept in the Site File and forwarded to GenePOC.

External control materials are provided by GenePOC. A reference GBS strain bearing the *cfb* gene (e.g. ATCC 12973) will be used as a positive external control (EC) while not inoculated Lim broth will be used as a negative EC.

6.5.1.2. Sample Processing Control

The Processing Control (PC) is incorporated into each microfluidic cartridges and is intended to monitor for the effectiveness of liquid displacement, sample treatment (Lysis) and heating during the sample processing steps. The PC also monitors the integrity of

the PCR reagents, the thermal cycling, and for the presence of inhibitory substances during the amplification and detection steps. A failed PC renders the sample Unresolved.

6.5.1.3. Monitoring for the Presence of DNA Contamination

At the request of the GenePOC Study Manager, the work area and equipment will be monitored for the presence of *Streptococcus agalactiae cfb* gene contamination using the GenePOC GBS test. Should contamination arise, the Study Manager will instruct the site on the measures to take prior to testing additional samples.

6.5.2 Reference Method

As determined by the Laboratory procedure, appropriate positive and negative external control (ECs) will be tested on regular basis for the reference method. These external controls results will need to be kept in the Site File and forwarded to GenePOC.

External control materials are provided by GenePOC. A reference GBS strain bearing the *cfb* gene (e.g. ATCC 12973) will be used as a positive external control (EC) while not inoculated Lim broth will be used as a negative EC.

6.6. Clinical Trial Quality Assurance

The following measures will be taken to assure the quality of the trial conduct and data.

6.6.1. Accountability of investigational Materials

The Clinical Center will account for all GenePOC GBS System investigational materials received from GenePOC. GenePOC clinical trial team will monitor site records for investigational materials accountability. All materials will be handled and disposed of according to Package Insert instructions, Study Site Manual or as directed by the GenePOC Study Manager. Upon completion of the study, all remaining supplies provided by GenePOC will be returned to GenePOC unless otherwise directed by the GenePOC Study Manager in writing.

6.6.2. Process for Protocol Changes and Deviations

6.6.2.1. Protocol Amendment

A Protocol Amendment is a change to, or clarification of, the Study Protocol which may impact the conduct and potential benefit of the study, or participant safety. For each protocol amendment, the GenePOC Study Manager will complete a Protocol Change Form. Protocol changes must be reviewed, approved and signed by the GenePOC Study Manager, a representative of GenePOC and the Principal Investigator. All changes to the Protocol must be submitted to the Clinical Center IEC for examination and approval (if required). The Principal Investigator will ensure that protocol changes are implemented after written approval by all parties (including the IEC if needed), that

all personnel using the protocol at the Clinical Center receive training for the change, and that the new protocol is maintained in the study records at the Clinical Center. Examples of such changes include, but are not limited to: the study objectives, study design, sample sizes, study procedures, or administrative aspects.

6.6.2.2. Protocol Deviations

Each protocol deviation reported to the GenePOC Study Manager by the Clinical Center, observed by the GenePOC Study Manager or CRA during monitoring contacts or visits, or observed through review of CRFs will be documented by the GenePOC Study Manager, CRA or Clinical Center personnel on a Protocol Deviation Form. The Protocol Deviation Form will contain the description of the deviation, the impact on the trial or subject enrollment, the impact to the affected data and any corrective action taken to conform to the protocol. All Protocol Deviation Forms will be reviewed and signed by the GenePOC Study Manager or CRA and either the Principal Investigator (if the Clinical Center was involved or concerned) or the GenePOC Clinical Operations Manager. A copy of each Protocol Deviation Form will be kept at the Clinical Center and the original at GenePOC.
Examples of such deviations include, but are not limited to:

- not completing the testing required by the protocol;
- enrolling inappropriate samples;
- failure to follow Package Insert instructions for use and storage of the investigational device;
- failure to follow the Reference Method (e.g. use of expired materials);
- failure to perform EC as directed;
- not respecting the time to perform testing or retesting.

Protocol deviations might render a data not eligible to be include in the final data analysis.

6.6.3. Methods to Assure Trial Consistency and Integrity: Monitoring and Auditing

Monitoring will be accomplished by telephone conversations and recorded on the Site contact log, written correspondence (including email and letters), and site visits recorded on the site visit log and Clinical Trial Monitoring Reports.

Periodic checks may be made with the Principal Investigator and/or his/her staff that will include availability of materials, subject and sample enrollment, product accountability, and clarification of any questions. These checks may be accomplished via telephone conversations and/or written communication (emails or letters/memos).

Telephone conversations will be documented by the GenePOC Study Manager and CRA (recorded on the site Contact log). Critical study communications imparted by telephone to Clinical Center personnel (including but not limited to new instructions or training, identification of non-conformities, deviations, corrective actions, or incidents)

will be followed up with a written communication to the Clinical Center. Copies of relevant written communication (including e-mails) will be kept by the GenePOC Study Manager and the Clinical Center.

Monitoring visits may include review of IEC review status, laboratory accreditation, subject enrollment status, regulatory requirements, study compliance, eCRF and source data, adverse event and incident reporting, and study materials storage and disposition. Protocol Change Forms and Protocol Deviation documentation should be reviewed as well as CRFs and applicable source data. Follow-up actions will be documented in writing to the Clinical Center.
The GenePOC CRA will arrange for correction of discrepancies, missing data, or omissions on CRFs by the Principal investigator or designee as appropriate.

The GenePOC Study Manager will maintain close liaison to clarify any problems that may arise, and to ensure that the study is being carried out according to this protocol. The Clinical Center shall permit the GenePOC CRA, and other GenePOC personnel as indicated, to visit the Clinical Center and audit or inspect the study records and materials, to determine Principal Investigator's compliance with the protocol, relevant guidelines and regulations for clinical trials.

7. DATA COLLECTION, MANAGEMENT AND REPORTING

7.1. Clinical Center Responsibility

7.1.1. General Instructions on Recording and Sending Data to GenePOC

An Electronic Data Capture (EDC) system will be used by all Clinical Centers.

Individual instructions for completing paper source documents, CRFs and other forms will be provided by GenePOC in the Training Manual.

Electronic media containing instrument data should be sent to GenePOC at least once per week. The Clinical Center must keep one of the instrument back-up media on site.

Test results should be entered in the eCRF promptly i.e. within 2 days of the test results are confirmed.

The following paper forms (but not limited to) will be completed as needed and kept on site during the study with a copy at GenePOC. The original will be kept at GenePOC at the end of the study with copies kept at the Clinical Center:

- Site Signature and Delegation of Responsibility Log (All persons authorized to complete, review and/or sign study documentation, including CRFs, will sign this Log.

- Study Visit Log;
- Reference method external control forms for culture media will be completed and copies will be sent to GenePOC with originals kept at the Clinical Center at the end of the study.
- Site Contact Log forms will be completed and maintained at the Clinical Center.

Paper source documents will be completed first then the data will be transferred to the eCRF.

7.1.1.1. Electronic Data Capture (EDC)

Electronic CRFs will have to be completed immediately (usually within 2 days of collection) following completion of the testing procedure.

The Principal Investigator must designate, in writing, any individuals authorized to complete and review the eCRFs. Only the Principal Investigator will have the right to sign the eCRFs.

7.1.2. Final Report

The Principal Investigator, with input from the laboratory personnel, will be asked to provide GenePOC with a final report of special study issues, findings, assessment of ease-of-use and workflow, and any problems or recommendations, within 30 days of completion or termination of the study. This final report may include the convenience (ergonomies, performance, utility, rapidity, etc.) of the GenePOC GBS System for integration into routine laboratory use and potential use near the patient.

7.2. GenePOC Responsibility

A termination letter or notice will be sent by GenePOC to the Principal Investigator notifying the Clinical Center of the successful completion of the study terms by the Clinical Center. Terms and notifications for other causes of study termination will be addressed in the Clinical Trial Agreement.

7.3. Data Confidentiality

GenePOC will maintain the security and confidentiality of all trial data sent to GenePOC. GenePOC and the Clinical Center may be required to provide regulatory agencies access to trial data and records. GenePOC trial databases will not be shared with any third party. GenePOC provides an assurance that the de-identified data obtained in this study will be safeguarded and not used for unauthorized purposes. All other agreements by GenePOC, the Principal Investigator, and the Clinical Center in regards to confidentiality may be found in the Confidential Disclosure Agreement and the Clinical Trial Agreement.

7.4. Data Verification and Validation Rules

Data captured will be entered into the database through the EDC system. Data related to CRF and accountability logs will be transferred from the paper CRFs (forms considered as source documents) to the eCRFs. Data related to the Reference Method, the discrepancy testing and EC will be transferred directly from the laboratory worksheets (considered as source documents) to the eCRFs.

Data will be managed and controlled following GenePOC Quality Procedures and stored in a secure database with limited access and with electronic audit trails.

Data validation (confirming the correctness, completeness, and compliance of the data) will be performed both during and after data entry. Validation during data entry will be performed using both visual inspection and programming incorporated into the forms. Post data entry validation procedures will be documented in the Forms Specifications and/or Post-Data Entry Processing documents, and will be performed at minimum prior to the final Data Analysis.

8. CLINICAL TRIAL INCIDENTS, RISK MANAGEMENT AND ADVERSE EVENTS

8.1. Clinical Trial Incidents

A Clinical Trial Incident is defined as any problem involving the investigational device, Reference Method, procedures, human subjects, or operators as a result of execution of this Study Protocol. Clinical Trial Incidents may adversely (or potentially adversely) affect human safety, the integrity of the evaluation data, or the operation of devices.

All serious occurrences which affect the health or safety of human subjects or operators involved in this evaluation are considered a Clinical Trial Incident, and may also be determined to be an Adverse Event. Adverse Events are addressed specifically in Section 8.4 below. Since patients are not directly affected by the diagnostic device under evaluation and results are not used for clinical decisions, virtually all Clinical Trial Incidents are not considered Adverse Events.

The Clinical Trials Incident Report Form is used to capture problems or observations arising during the use of the investigational product or in the execution of this Study Protocol and should be reported to the GenePOC Study Manager. The form should be filled out with a full description of the incident, and sent by fax to the GenePOC Study Manager. Incidents might include but are not limited to such occurrences as: instrument failure (IND or other), run incomplete (NA or other), damage or deterioration of the GenePOC GBS System, damage to devices or packaging caused by shipping or

handling, or other incidents deemed to be failures or problems with the product or the execution of this Study Protocol.

8.2. Reporting of Incidents

Any incidents which occur during the use of the GenePOC-GBS System or execution of this Study Protocol must be reported immediately to GenePOC.
The primary contact will be the Study Manager.

Rachelle Nadeau	Phone	(418) 650-3535 #254
Study Manager	e-mail	rachelle.nadeau@genepoc.ca

In case of a problem with the GENEPOC™ instrument, the second line of support will be GenePOC:

Sébastien Chapdelaine	Phone	(418) 650-3535 #221
Vice President Research & Development	Cell Phone e-mail	(418) 803-0650 sebastien.chapdelaine@genepoc.ca

The Clinical Center must identify itself as a GenePOC GBS clinical trial site and by providing it site number

In case of a problem with the EDC System, contact the first line of support listed above who will either address the problem or dispatch the problem, as needed, to the Data Manager or the EDC System support line.

All incidents must be documented on a Clinical Trial Incident report form.

8.3. Risk Management

8.3.1. Potential Risks to the Patient

There are no risks to the patient inherent to the execution of this evaluation; the investigational testing will:

1) Be performed on excess de-identified samples only; and,
2) Include parallel clinical routine testing by an approved and established method for reporting patient results.

8.3.2. Potential Risks to the Personnel operating the Product

To reduce the risk of exposed personnel, all processing, testing, and culturing of potentially infectious samples must always be performed according to Standard Precautions, CDC Guidelines, Standard Guidelines, and the Clinical Center's own

Laboratory Safety procedures and policies.

8.4. Adverse Events

- An Adverse Event (AE) is defined as any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons (investigational devices only) which is associated with the use of an investigational product or participation in an investigation, whether or not related to the investigational medical device. This includes event not seen at baseline and event that if present at baseline have worsened in intensity.
- Anticipated adverse events are defined as adverse events that are already known to occur from past experience. However, as cited in Section 8.1 above, there are no anticipated adverse events associated with this Study Protocol.
- An Adverse Device Effect is defined as an adverse event related to the use of an investigational medical device.
- A Serious Adverse Device Effect is defined as any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device.
- An Unanticipated Serious Adverse Device Effect is a Serious Adverse Device Effect for which the effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.
- If an Unanticipated Serious Adverse Device Effect occurs, it must be reported immediately by the Principal investigator to GenePOC and to the IEC (when required). GenePOC may additionally be required to report the occurrence to regulatory authorities.
- Medical Device Reporting (MDR) - Any commercially marketed device used in the trial which causes or contributes to a death or serious injury must be additionally reported to the commercial manufacturer as an MDR reportable event, under US federal regulations and Health Canada. An occurrence of serious injury during the trial that resulted from the use of a marketed device may require reporting as both an Adverse Event (to the IEC and Sponsor of the trial) and as an MDR (to the commercial manufacturer of the device).

9. REGULATORY AND ADMINISTRATIVE INFORMATION

9.1. Institutional Requirements

The Study Protocol must be submitted for review to the Clinical Center's IEC prior to the start of the study. In addition, this committee will inform the Principal

investigator and the sponsor as to whether a waiver of informed consent has been granted.

This must be done in accordance with Part 56 (Institutional Review Boards) of the Code of Federal Regulations Title 21 (USA) and Section 81(k) of the Canadian Medical Device Regulations.

A copy of the IEC acknowledgment of review or approval from each institution must be forwarded to the study sponsor, GenePOC.

9.2. Ethical Conduct and Good Clinical Practice

The procedures set forth in this Study Protocol are designed to ensure that GenePOC and the clinical investigators abide by the principles of Parts 50 and 56 of the Code of Federal Regulations Title 21 (USA), the Tri-Council's Code of Ethical Conduct for Research involving Humans (1998) and Part 3 of the Medical Devices Regulations (Canada), the Declaration of Helsinki (USA and Canada), and the Good Clinical Practices (ICH: USA, Canada and Europe), in the conduct, evaluation and documentation of this study.

9.3. Investigator Responsibilities

The investigator responsibilities are defined in the present Study Protocol. The Financial Disclosure certification must be filled out in accordance with Part 54 of the Code of Federal Regulations, Title 21.

9.4. Patient Information Confidentiality

All information will be treated with the utmost confidentiality by the hospital and the study sponsor, GenePOC. Only de-identified data will be obtained. Patient names or medical record numbers will not be transferred to the study sponsor.

The samples will be used strictly for isolation of *Streptococcus agalactiae* in culture, and for no other purposes. Results from this study may be used by GenePOC to fulfill regulatory requirements of Health Canada, the US Food and Drug Administration (FDA), the European Parliament (providing the CE marking) and rest of the world.

9.5. Data Maintenance and Disclosure

Study binder(s) will be provided to each Clinical Center to organize the required study documentation. Each Clinical Center is directly responsible for the maintenance and organization of the study documentation.

Any corrections and/or changes made to entries on paper forms or logs, by the Principal Investigator or designees, must be crossed out with a single line leaving the initial entry legible. The correction must be dated and initialed. Incorrect entries

must not be covered with correction fluid, obliterated, or made illegible in any way. If the reason for the change is not obvious, an explanation for the change must be written next to the modification.

Any change performed on an electronic form will be audited by the system and, when required, justified before electronic signature.

The investigator is obligated to provide the study sponsor with complete test results and all data derived from the study. Any information that is unclear will be brought to the attention of the Principal Investigator and/or laboratory contact for prompt resolution.

9.6. Clinical Center Compliance

9.6.1. Investigator Responsibility

Data generated from this evaluation will be used to support regulatory submissions. The Principal Investigator is expected to ensure that the Clinical Center and its personnel comply with Good Clinical Practices and pertinent regulations governing clinical research.

9.6.2. Accountability of Materials

All materials will be handled and disposed of according to manufacturer's instructions. All investigational devices and their use and disposal will be accounted for in writing. Upon completion of the study, all remaining devices provided by GenePOC will be returned to GenePOC unless otherwise directed by the GenePOC Study Manager in writing.

9.6.3. Retention of Records

The Principal Investigator will retain trial related documents as required by the applicable regulatory requirements or by an agreement with GenePOC. The Principal Investigator should take measures to prevent accidental or premature destruction of these documents. Essential documents should be retained for:

- A period of five years after the last approval or a marketing application to regulatory agencies.
- A period of five years has elapsed since the formal discontinuation of development of the investigational product.

9.7. Trial management

9.7.1. Study Initiation

The Clinical study is anticipated to start in January 2016 at the earliest. Sample enrollment will begin upon signed approval of all contract trial agreements, receipt of written IEC acknowledgment of review of this Study Protocol and demonstration of proficiency. The study is expected to be conducted over a period of eight (8) weeks

depending upon the enrollment rate of diagnostic samples and the prevalence of *Streptococcus agalactiae.*

9.7.2. Study Extension

The evaluation may be extended beyond the estimated duration under terms agreed upon by the Clinical Center and GenePOC if more data are required for product development, or if the study is redirected or re-initiated. Any redirection of the study or re-initiation after a period of suspension would be subject to the re-negotiation of terms between GenePOC and the Clinical Center.

9.7.3. Rules for Discontinuation

GenePOC retains the right to terminate or curtail the study if this study protocol is not followed, or if the device under evaluation requires further development to meet the intended clinical objectives.

The Clinical Center shall terminate the study upon any of the following conditions:

- Completion of the agreed maximum number of positive results or the agreed maximum number of total samples;
- Reaching the date of maximum study duration;
- Withdrawal of approval from the Clinical Center Administration or IEC.

Other reasons and conditions for study termination could be addressed in the Clinical Trial Agreement.

10. REFERENCES

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4. Schuchat, A., Epidemiology of group B streptococcal disease in the United States: shifting paradigms. Clin Microbiol Rev, 1998. 11(3): p. 497-513.
5. CDC and C.f.D.C.a. Prevention of perinatal group B streptococcal disease: a public health perspective. Revised Guidelines. Morbid Mortal Weekly Rep2010. 595: p. 1-32.
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11. APPENDIX

11.1. APPENDIX A:

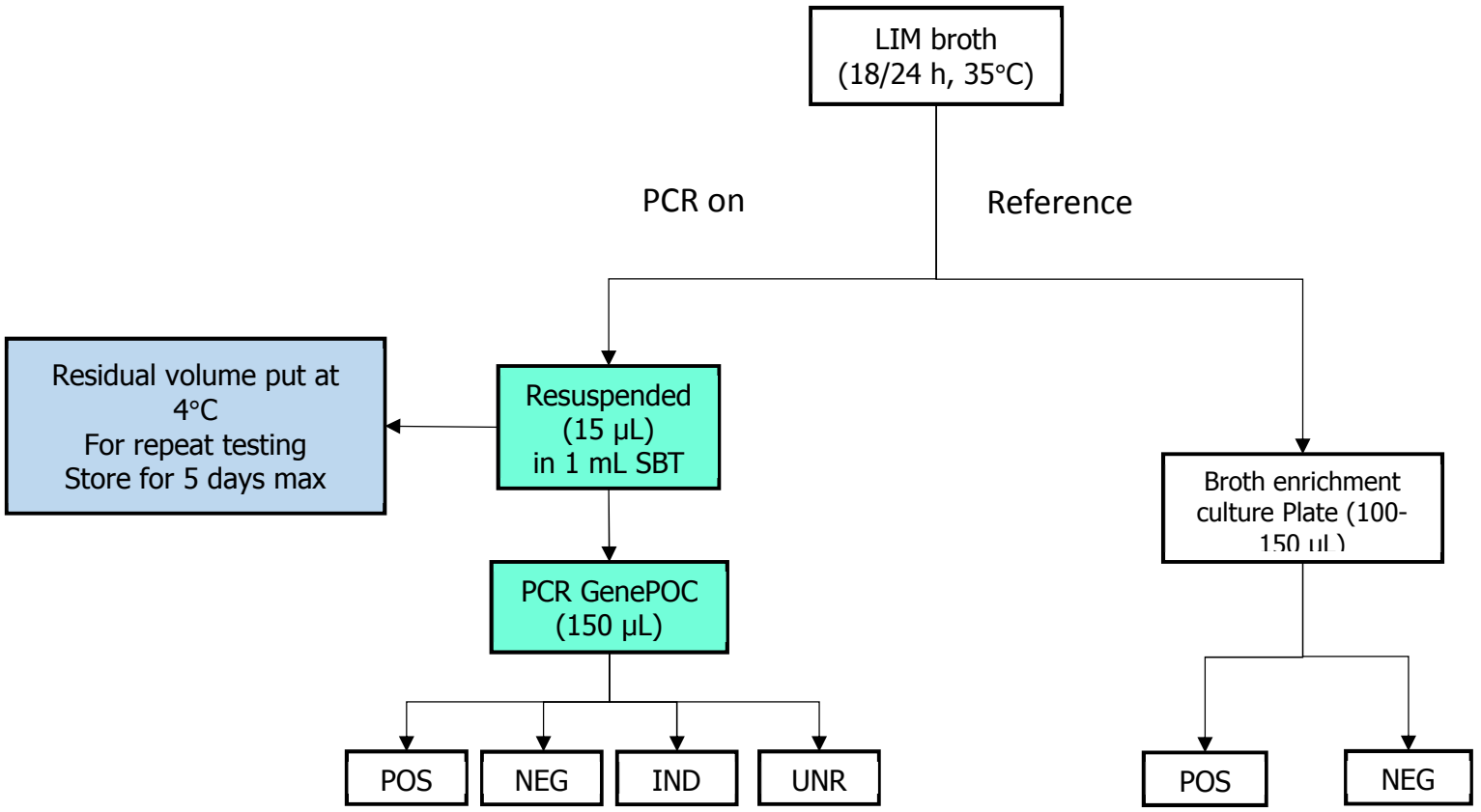
Clinical Investigation Requirements Relating to Each Clinical Center

Trial Requirements	Investigator	Sponsor
Confidential Disclosure Agreement: CDA	Sign agreement and keep one of the originals in the investigator Site Files	Keep one of the originals in the Trial Master Files
Curriculum vitae of principal investigator, co-investigators and other key site personnel	Keep a copy in the investigator Site Files	Keep a copy in the Trial Master Files
Study training records	Keep a copy in the investigator Site Files	Keep the original in the Trial Master Files
Laboratory Certification	Keep a copy in the investigator Site Files	Keep a copy in the Trial Master Files
Protocol, including any revisions and changes	Sign, date and keep one of the originals in the investigator Site Files	Sign, date and keep one of the originals in the Trial Master Files
CTA and Financial Agreement	Sign, date and keep one of the originals in the investigator Site Files or in the investigator's files	Sign, date and keep one of the originals in the Trial Master Files
IEC composition, approval notification(s), annual reports, correspondence, including notices of amendments deviations and incidents. **Or** IEC acknowledgment of review	Submit file to applicable committee. Keep the originals In the investigator Site Files and send a copy to the sponsor	Keep a copy in the Trial Master Files
Financial Disclosure Agreement and Updates	Sign agreement and keep one of the originals in the investigator Site Files	Keep one of the originals in the Trial Master Files
Site Contact Log	No Copy	Fill out and keep the original in the investigator Site Files
Site Signature and Delegation of Authority Log and Study Visit Log	Fill out when necessary, keep original in the investigator Site Files during the study and send original to the sponsor at the end of the study.	Keep a copy during the study and the original at the end of the study in the Trial Master Files.
Clinical Trial Incident Report form	Fill out, sign and keep original in the investigator Site Files and send copy to the sponsor	Keep a copy in the Trial Master Files
Laboratory Worksheets	Fill out, keep a copy in the investigator Site Files and send original to the sponsor once or twice per week	Keep the original in the Trial Master Files
Paper CRFs and paper EC Form	Fill out, sign, keep a copy in the investigator Site Files and send originals to the sponsor once or twice per week	Keep originals in the Trial Master Files or other data binder
Reference method external control forms	Keep the originals in the Investigator Site Files or Laboratory Files	Keep a copy of each in the Trial Master Files

Trial Requirements	Investigator	Sponsor
Investigational Material Accountability Log	Keep a copy in the investigator Site Files and send originals to the sponsor every two weeks or when completed.	Keep the originals in the Trial Master Files
Data Clarification Forms	Fill out, keep a copy in the investigator Site Files and send originals to the sponsor	Keep originals in the Trial Master Files or other data binder
Relevant Communications	Keep a copy in the investigator Site Files printed and/or on a CD.	Keep a copy in the Trial Master Files or other data binder printed and/or on a CD.
USB Keys for runs	Export daily runs from the GenePOC instrument. keep on site for all Instrument backups.	Transfer electronically onto server and keep on a CD after.

11.2. APPENDIX B:

Testing Algorithm



11.3. APPENDIX C:

Discrepant Testing Algorithm