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## PROTOCOL SIGNATURE PAGE

# A Study of the Clinical Utility of Point of Care **cobas® liat** CT/NG/MG nucleic acid test Versus Current Standard Practice

Protocol No. LIA-STI-542

I have read this study protocol. I agree to make available to the sponsor, Roche Molecular Systems, Inc. (or its designee), original source documents and all regulatory documents pertaining to this study.

By my signature below, I agree to conduct this study in accordance with this study protocol, standard laboratory practices, local laws, and federal regulations as described in this study protocol, and to cooperate fully with the sponsor in the conduct of study-related audits.

\_\_\_\_\_  
Principal Investigator Name (Print)

\_\_\_\_\_  
Principal Investigator Signature

\_\_\_\_\_  
Date

## CLINICAL STUDY PROTOCOL

# A Study of the Clinical Utility of Point of Care **cobas® liat** CT/NG/MG nucleic acid test Versus Current Standard Practice

Roche Molecular Systems, Inc.  
Pleasanton, California 94588

Protocol No. LIA-STI-542  
Internal Unique Study Number: RD006616

**Note:** *The information contained in this protocol is the property of Roche Molecular Systems, Inc. (RMS). The information is confidential and is to be used only in connection with matters authorized by RMS; no part of this protocol is to be disclosed to others (orally, in writing, and/or distributed) without written permission from RMS.*

The **cobas® liat** CT/NG/MG nucleic acid test is an Investigational Device Limited by US Federal Law to Investigational Use. The performance characteristics of this product have not been established.

## VERSION HISTORY

| Version Number | Description                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1              | Initial release                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| 2              | <ul style="list-style-type: none"><li>- Updated product name based new branding throughout document. Deleted footnotes pertaining to planned rebranding, as rebranding has already occurred.</li><li>- Updated product name in the proposed Intended Use Statement with the new product branding.</li><li>- Added additional exclusion criteria to the synopsis and to Section 10.2.</li><li>- Added statements throughout to clarify that the external laboratory PCR testing will be performed at a CLIA-certified reference laboratory</li><li>- Added an additional term to the Glossary</li><li>- Deleted repetitive test regarding printout of diagnostic results from Section 8.2 as it is covered in Section 16.1. Moved and merged text pertaining to detected, not detected and invalid POC test/re-test results from Section 8.2 into Section 11.1.</li><li>- Edits to Section 17.2.3, Exploratory Analyses, for clarity.</li></ul> |
| 3              | <ul style="list-style-type: none"><li>- Revised the inclusion criteria. Participants will need to be at least 18 years of age.</li></ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |

## PROTOCOL SYNOPSIS

| Section                             | Description                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|-------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Title                               | A Study of the Clinical Utility of Point of Care <b>cobas® liat</b> CT/NG/MG nucleic acid test Versus Current Standard Practice                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| Protocol No.                        | LIA-STI-542                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Study Identifier                    | RD006616                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| Sponsor                             | Roche Molecular Systems, Inc.<br>4300 Hacienda Drive<br>Pleasanton, California 94588<br>Telephone: 925.730.8000                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| Sponsor Organization Type           | Diagnostic Industry                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| Sponsor Representative and Contact  | [REDACTED], MD<br>Roche Molecular Systems, Inc.<br>4300 Hacienda Drive<br>Pleasanton, CA 94588<br>Cell phone: [REDACTED]<br>E-mail: [REDACTED]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| Principal Investigator/Investigator | An updated list of principal investigator and Investigators, study sites, and institutions will be maintained throughout the study in the sponsor's study file. The definitive list will be provided in the study report.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| Investigational Product             | <b>cobas® liat</b> CT/NG/MG nucleic acid test ( <i>hereafter, referred to as 'cobas® liat CT/NG/MG'</i> )                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| Proposed Intended Use               | <p>The <b>cobas® liat</b> CT/NG/MG nucleic acid test is an automated, qualitative <i>in vitro</i> nucleic acid diagnostic test that utilizes real-time polymerase chain reaction (PCR) for the direct detection of <i>Chlamydia trachomatis</i> (CT), <i>Neisseria gonorrhoeae</i> (NG), and <i>Mycoplasma genitalium</i> (MG) nucleic acid in male/female urine and vaginal swabs (clinician-collected and self-collected), both in <b>cobas®</b> PCR Media (Roche Molecular Systems, Inc.).</p> <p>This test is intended for professional use in a clinical laboratory setting or point-of-care (POC) location as an aid in the diagnosis of urogenital infections in both symptomatic and asymptomatic individuals.</p> |
| Study Design                        | A block randomized, controlled 2-arm prospective study                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| Study Purpose Summary               | This study is designed to assess the comparative clinical utility of point of care <b>cobas® liat</b> CT/NG/MG to the current standard practices                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| Study Objective                     | <b>Primary Objectives:</b><br>The primary objective of this study is to compare the clinical impact of rapid POC testing using the <b>cobas® liat</b> CT/NG/MG test with the standard of care                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |

| Section                      | Description                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                              | <p>(SOC)<sup>1</sup> for managing participants at increased risk of STIs (symptomatic and/or known STI contact). This will be expressed in terms of degree of inappropriate treatment (the primary outcome) on the same day as the medical encounter, based on a composite measure reflecting CT, NG, and/or MG presence combined. An inappropriate treatment is defined as under and/or overtreatment on the day of the medical encounter based on Centers for Disease Control and Prevention (CDC) recommendations for the pathogen-specific results obtained by the external laboratory PCR (EL-PCR) testing. Furthermore, overtreatment is defined by the provision of 2 or more antibiotics when only 1 is necessary, or, provision of any unnecessary antibiotics; undertreatment is defined by failure to provide pathogen-appropriate antimicrobials either alone or in combination.</p> <p><b>Secondary Objectives:</b></p> <p>The secondary objective will be subset analyses of inappropriate treatment for each pathogen individually.</p> <p>Other secondary outcomes that may be addressed, but will not be limited to, time utilization by clinician and participants, rate of participant follow-up, predicted healthcare costs, resource utilization, clinician and participant confidence, and clinician and participant satisfaction.</p> <p>These data will not be used to achieve regulatory clearance and the Clinical Laboratory Improvement Amendments waiver.</p> |
| Samples                      | Urine and/or vaginal samples of approximately 348 enrolled participants will be collected to randomize a minimum of 174 participants to each arm; POC and SOC.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| Study Duration               | 3-4 months                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Inclusion/Exclusion Criteria | <p><b>Inclusion Criteria:</b></p> <p>Participants will be required to meet all of the following criteria for enrollment:</p> <ul style="list-style-type: none"> <li>• Sexually active people ≥18 years of age</li> <li>• Willing and able to provide written, informed consent (according to the Institutional Review Board [IRB] at the respective sites)</li> <li>• People seeking medical services for symptoms consistent with an STI and/or known exposure to an STI</li> </ul> <p><b>Exclusion Criteria:</b></p> <p>Participants, regardless of symptom status, will be excluded from enrollment if any of the following criteria are met:</p> <ul style="list-style-type: none"> <li>• Previously enrolled in the study</li> <li>• Unable to provide informed consent</li> <li>• Currently pregnant</li> <li>• Declines POC testing</li> <li>• Presents for routine STI screening (asymptomatic)</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |

<sup>1</sup> SOC is often used as legal terminology in medicolegal settings. In the context of this study, SOC is defined as the traditional/typical diagnosis and treatment steps in practice recommended by the Centers for Disease Control and Prevention (CDC) guidelines that rely upon clinical syndromic presentations and/or external laboratory testing (not point-of-care testing for CT, NG, and MG), and which typically requires 2 or more days turnaround time for clinicians.

| Section                                       | Description                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|-----------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                               | <ul style="list-style-type: none"> <li>• Use of antimicrobial agents active against CT, NG, or MG during the 21 days period before sample collection. Example of such antimicrobial agents include the following: <ul style="list-style-type: none"> <li>– Macrolides (eg, azithromycin and erythromycin)</li> <li>– Penicillins (eg, amoxicillin)</li> <li>– Tetracyclines (eg, doxycycline)</li> <li>– Fluoroquinolones (eg, ciprofloxacin, ofloxacin, levofloxacin, and moxifloxacin)</li> <li>– Cephalosporins (eg, ceftriaxone and cefixime)</li> </ul> </li> <li>• Use of phenazopyridine-containing urinary pain relief medicines (ie, Azo or Pyridium) within 2 days prior to sample collection</li> <li>• Use of any over-the-counter feminine hygiene products (internally or externally), such as vaginal moisturizers, lubricants (e.g., Replens, RepHresh, etc.), and feminine washes/vaginal douches, etc. within the 3 days prior to sample collection. The use of tampons or pads during menses is not an exclusionary criterion.</li> <li>• Contraindication to vaginal swab sampling where vaginal swab sampling is the only option available</li> <li>• Urination within 1 hour prior to sample collection (for subjects providing urine sample)</li> </ul> |
| Follow-up of participants providing specimens | None.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Compliance Statement                          | This study will be conducted in compliance with the protocol, the International Conference on Harmonization (ICH) Good Clinical Practice Guidelines, the Declaration of Helsinki, regulations of the US Food and Drug Administration (FDA), and applicable local regulations.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |

## GLOSSARY

| Term                        | Description                                                                                                        |
|-----------------------------|--------------------------------------------------------------------------------------------------------------------|
| ADE                         | adverse device effect                                                                                              |
| AE                          | adverse event                                                                                                      |
| CDC                         | Centers for Disease Control and Prevention                                                                         |
| <b>cobas® liat</b> CT/NG/MG | <b>cobas® liat</b> CT/NG/MG nucleic acid test                                                                      |
| CSDT-Q                      | Clinician Satisfaction with Diagnostic Test Questionnaire                                                          |
| CT                          | <i>Chlamydia trachomatis</i>                                                                                       |
| DD                          | device deficiency                                                                                                  |
| DTS                         | Data Transfer Specification                                                                                        |
| eCRF                        | electronic case report form                                                                                        |
| EL-PCR                      | external laboratory-polymerase chain reaction                                                                      |
| FDA                         | US Food and Drug Administration                                                                                    |
| ICF                         | Informed consent form                                                                                              |
| IEC                         | Independent Ethics Committee                                                                                       |
| IRB                         | Institutional Review Board                                                                                         |
| IVD                         | in vitro diagnostic                                                                                                |
| MG                          | <i>Mycoplasma genitalium</i>                                                                                       |
| NAAT                        | nucleic acid amplification test                                                                                    |
| NG                          | <i>Neisseria gonorrhoeae</i>                                                                                       |
| OT                          | overtreatment                                                                                                      |
| Participant                 | A patient (or subject) who has provided informed consent to participate in the study                               |
| PSDT-Q                      | Patient Satisfaction with Diagnostic Test Questionnaire                                                            |
| PCR                         | polymerase chain reaction                                                                                          |
| PMP                         | patient management plan                                                                                            |
| POC                         | point of care                                                                                                      |
| POC test                    | In this study protocol the point of care test is referring to the ' <b>cobas® liat</b> CT/NG/MG nucleic acid test' |
| RMS                         | Roche Molecular Systems, Inc.                                                                                      |
| SADE                        | Serious adverse device effect                                                                                      |
| SAE                         | serious adverse event                                                                                              |
| SAS                         | statistical analysis software                                                                                      |
| SOC                         | standard of care                                                                                                   |
| STI                         | sexually transmitted infection                                                                                     |
| UT                          | undertreatment                                                                                                     |
| US                          | United States                                                                                                      |

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## 1. PRINCIPAL INVESTIGATOR AND SITE INFORMATION

Information regarding participating sites and investigators will be available in the electronic trial master file at Roche Molecular Systems, Inc. (RMS) and in the final clinical study report.

## 2. ROCHE MOLECULAR SYSTEMS, INC. CONTACT PERSONNEL

Questions regarding this protocol or any aspect of the study may be directed to the following RMS personnel:

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Pleasanton, CA 94588

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E-mail: [REDACTED]

For unanticipated serious adverse events and serious adverse device effects related to this protocol, contact the study manager (listed above) and the medical monitor:

## Medical Monitor

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### 3. INTRODUCTION

Urogenital infections such as urethritis and cervicitis are common clinical manifestations of sexually transmitted bacteria *Chlamydia trachomatis* (CT), *Neisseria gonorrhoeae* (NG), and *Mycoplasma genitalium* (MG).<sup>1</sup> Although patients with these infections sometimes present with clinical symptoms (such as dysuria, discharge, or pain), a majority will be asymptomatic and therefore unsuspecting.<sup>1,2</sup> CT and NG are among the most frequent causes of sexually transmitted infections (STIs), with an estimated global annual incidence above 131 million and 78 million, respectively.<sup>3,4</sup> In addition to CT and NG, MG has emerged as an important cause of urogenital infections in both men and women,<sup>5,6</sup> leading to the development of new testing guidelines in Australia and Europe,<sup>7,8</sup> as well as the recent approval of new MG detection tests in the United States (US) and beyond, globally. In men alone, MG is estimated to cause between 10% to 35% of cases of non-gonococcal non-chlamydial urethritis.<sup>8</sup> If left undiagnosed and untreated, urogenital infections caused by CT, NG, and MG can cause pelvic inflammatory disease, ectopic pregnancy, infertility, stillbirths, epididymitis, urethral stricture, prostatitis, and psychosocial harm,<sup>1,2,9-12</sup> exerting a severe burden on the health and economy of the world.<sup>13,14</sup>

Antibiotic management and resistance patterns differ for CT, NG, and MG,<sup>2,10</sup> however, these pathogens present with similar clinical signs and symptoms and can only be distinguished with etiological (or microbiological) testing. Clinical syndromic management algorithms, which enable empiric treatment without etiological testing through the identification of clinical “syndromes” (ie, consistent patterns of symptoms and easily recognized signs),<sup>15</sup> are both imprecise and inconsistent.<sup>16,17</sup> Etiological diagnosis is therefore essential; however, widely

available non-molecular test options (such as microscopy, immunoassays, and culture) are limited by poor performance or prohibitively long turnaround times.<sup>18,19</sup> Recently, molecular approaches using nucleic acid amplification test (NAAT) technologies have been endorsed as the preferred etiologic test for both CT and NG infections,<sup>20</sup> and serve as the only reliable diagnostic modality to detect MG (due to the poor sensitivity of cell culture and serological testing for MG).<sup>1,8</sup> More optimal clinical test performance, automation, and ease of specimen transport of NAATs have transformed laboratory-based testing capabilities and replaced time-intensive, culture-based methods.<sup>4,20,21</sup>

To complement important laboratory-based molecular solutions, a fast, accurate, and user-friendly diagnostic solution for CT, NG, and MG is needed at the clinical point of care (POC) to enable more rapid pathogen identification and treatment.<sup>22,23</sup> Rapid and accurate diagnosis within a single patient visit can both expedite accurate treatment and reduce the need for patient follow-up,<sup>23</sup> while simultaneously diminishing the potential for disease transmission, misdiagnosis, and inappropriate antibiotic use, all of which contribute to the progression of antibiotic resistance.<sup>24</sup> Resistance of NG to multiple antibiotics<sup>25</sup> and rapid emergence of MG resistance<sup>5</sup> are global threats that necessitate fast and highly accurate POC diagnostic testing capabilities.<sup>25</sup> Effective and rapid diagnosis at the POC may also alleviate psychological consequences that often accompany STI testing, such as shame, anxiety, stigma, and—in the case of vaginal swab—fear of discomfort commonly associated with sample collection.<sup>26</sup> Although there are many options for specimen collection in all genders, vaginal swabs and urine have emerged as preferred sample types that negate the need for invasive examination and enable self-collection by patients.<sup>18</sup> Self-collected vaginal swabs have been shown to perform similarly to clinician-collected or more invasive cervical<sup>18,27</sup> and endocervical swab<sup>27</sup> collection. Similarly, the performance of urine NAAT testing has been found to be comparable to vaginal swabs in selected testing populations<sup>18</sup> and overall may be a preferred sample type for POC testing in women owing to its ease of collection and use.

The use of extra-genital specimens (oropharyngeal and anorectal swabs) are out of scope for this study. It is acknowledged in the 2021 STI Treatment guidelines that extra-genital, in addition to urogenital specimens are important for CT and NG testing.<sup>1</sup> However, the clinical utility of

extra-genital specimen testing for MG are still largely unknown and therefore these specimen types are not included in this study.

The **cobas® liat** CT/NG/MG nucleic acid test (**cobas® liat** CT/NG/MG) uses real-time polymerase chain reaction (RT-PCR) technology to rapidly (approximately 20 minutes) and simultaneously detect and differentiate between CT, NG, and MG in easy-to-collect urogenital specimens (both urine and vaginal swabs) from symptomatic and asymptomatic individuals. The **cobas® liat** system instruments automation, small footprint, and easy-to-use interface enables this test to be performed both in sophisticated laboratory environments and as a POC tool in typical clinical settings such as physician offices, urgent care centers, specialty clinics, and emergency rooms. The simultaneous POC detection of CT, NG, and MG infections, by means of the CT/NG/MG test on **cobas® liat** system, will help diagnosis, treatment, infection reporting, patient education, and expedited partner therapy in patients with sexually transmitted urogenital infections to be readily accomplished during a single patient visit.

#### 4. PRODUCT PROPOSED INTENDED USE

The **cobas® liat** CT/NG/MG nucleic acid test is an automated, qualitative *in vitro* nucleic acid diagnostic test that utilizes real-time polymerase chain reaction (PCR) for the direct detection of *Chlamydia trachomatis* (CT), *Neisseria gonorrhoeae* (NG), and *Mycoplasma genitalium* (MG) nucleic acid in male/female urine and vaginal swabs (clinician-collected or self-collected), both in **cobas®** PCR Media (Roche Molecular Systems, Inc.).

This test is intended for professional use in a clinical laboratory setting or point-of-care (POC) location as an aid in the diagnosis of urogenital infections in both symptomatic and asymptomatic individuals.

## 5. STUDY OBJECTIVE

### Primary Objective

The primary objective of this study is to compare the clinical impact of rapid POC testing using the **cobas® liat** CT/NG/MG test with the standard of care (SOC)<sup>2</sup> for managing participants at increased risk of STIs (symptomatic and/or known STI contact). This will be expressed in terms of degree of inappropriate treatment (the primary outcome) on the same day as the medical encounter, based on a composite measure reflecting CT, NG, and/or MG presence combined. An inappropriate treatment is defined as under and/or overtreatment on the day of the medical encounter based on Centers for Disease Control and Prevention (CDC) recommendations for the pathogen-specific results obtained by external laboratory PCR (EL-PCR) testing at a CLIA-certified reference laboratory. Furthermore, overtreatment is defined by the provision of 2 or more antibiotics when only 1 is necessary, or, provision of any unnecessary antibiotics; undertreatment is defined by failure to provide pathogen-appropriate antimicrobials either alone or in combination.

### Secondary Objectives

The secondary objective will be subset analyses of inappropriate treatment for each pathogen individually.

Other secondary outcomes that may be addressed, but will not be limited to, time utilization by clinician and participants, rate of participant follow-up, predicted healthcare costs, resource utilization, clinician and participant confidence, and clinician and participant satisfaction.

These data will not be used to achieve regulatory clearance and the Clinical Laboratory Improvement Amendments waiver.

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<sup>2</sup> SOC is often used as legal terminology in medicolegal settings. In the context of this study, SOC is defined as the traditional/typical diagnosis and treatment steps in practice recommended by the Centers for Disease Control and Prevention (CDC) guidelines, that rely upon clinical syndromic presentations and/or external laboratory testing (not point-of-care testing for CT, NG, and MG), and which typically requires 2 or more days turnaround time for clinicians.

## 6. STUDY DESIGN

The study is designed as a block randomized, controlled 2-arm prospective study. The study targets to enroll approximately 348 participants at increased risk of STIs—participants who have known contact with CT/NG/MG (including participants who report knowledge or suspicion of STI exposure, despite the uncertainty of the specific STI pathogen or contact testing results), or participants with symptoms suggestive of STI—to participate in this study. Participants who give consent will provide demographic information and urogenital specimen(s) for CT/NG/MG testing on the **cobas® liat** system and for EL-PCR testing. Participants will be randomized in a 1:1 ratio in blocks (of multiples of 2) stratified by the site to either of the following arms:

- Standard of Care (SOC)
- Point of Care (POC)

In both arms, the clinician will see and evaluate the participant and will complete a standardized form, known as a patient management plan (PMP) ([Appendix 1](#)), at the conclusion of the participant's encounter. The critical difference between the arms is that the clinician in the POC arm will be provided POC test results upon which they may choose to base their clinical decisions, whereas the SOC arm will not receive POC test results.

The PMP identifies in a 'check-the-box' fashion a variety of pertinent information including:

- the pathogen(s) for which the clinician is recommending treatment
- recommended treatment(s) for the participant
- recommended treatment(s) for partner(s)/contacts(s)
- clinician-ordered testing
- additional interventions
- follow-up plans (e.g., return office visit, phone call)

The data collected from the SOC PMP (control data) and the POC PMP (interventional data) will be compared. An inappropriate treatment is defined as under and/or overtreatment on the day of the medical encounter based on Centers for Disease Control and Prevention (CDC)

recommendations for the pathogen-specific results obtained by EL-PCR. In this study, the EL-PCR will be conducted off-site for all the participants enrolled in the study at a CLIA-certified reference laboratory using the Roche **cobas®** CT/NG and the Roche **cobas®** TV/MG tests; both are validated and US Food and Drug Administration (FDA)-approved polymerase chain reaction (PCR)-based tests. In the case of co-infections, inappropriate/appropriate treatments will be assessed independently for each pathogen.

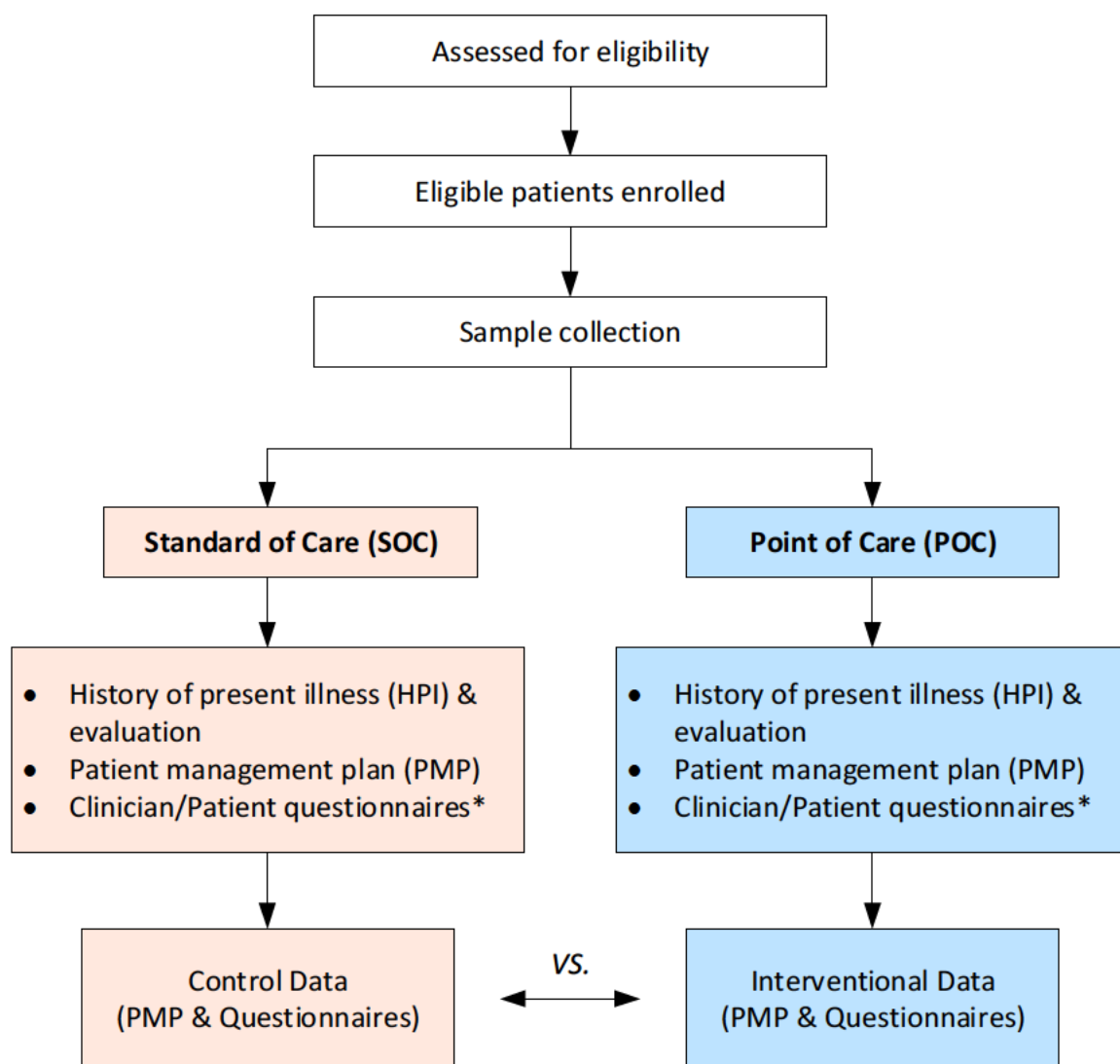
All participants will complete a patient questionnaire on-site after their medical visit. The questionnaire will measure participants' overall satisfaction with the medical visit, and their satisfaction with the diagnostic test, using the Patient Satisfaction with Diagnostic Test Questionnaire (PSDT-Q). For administration of the patient questionnaire to each participant, the study site will select either the Patient Questionnaire - Point of Care Version ([Appendix 2](#)) or Patient Questionnaire – Standard of Care Version ([Appendix 3](#)), based on the participant's assigned study arm. The versions differ only in their instructions which describe the test being evaluated.

All clinicians involved in the study will complete a clinician questionnaire ([Appendix 4](#)), the Clinician Satisfaction with Diagnostic Test Questionnaire (CSDT-Q), which assesses satisfaction with the diagnostic test (**cobas® liat** CT/NG/MG) compared with standard care. For this study, 'clinician' refers to any health care professional (e.g., doctor, provider, pharmacist, nurse, etc.) involved with performing diagnostic tests on participants, interpreting the results, and providing participant care. Study sites will identify the clinicians involved in the study then send out the satisfaction questionnaire to be completed by all study clinicians biweekly for the duration of the study period.

Test operators will not complete the CSDT-Q. Operators will complete a separate user experience questionnaire that will be administered biweekly for the duration of the study period.

The PMPs and satisfaction questionnaires will be "independent" of the electronic medical record (EMR) and anonymized. All data for this study will be derived from the PMPs and questionnaires filled out by the respective participants, and the anonymized EL-PCR testing results.

**Figure 1: Study Design**



\*Participants will complete a questionnaire after their medical visit. Clinicians will complete the Clinician Satisfaction with Diagnostic Test Questionnaire biweekly for the duration of the study period.

## 7. ETHICS AND COMPLIANCE

This study will be conducted in compliance with the protocol, applicable International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guidelines for Good Clinical Practice (GCP), FDA regulations, and the Declaration of Helsinki,

data privacy laws (e.g., HIPAA), and applicable national regulations or laws of the country in which or for which the study is conducted.

### **7.1. Ethics Committee Review and Approval**

Before the start of the study, the study protocol will be submitted to an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) in accordance with FDA and local regulatory requirements. The study shall not begin until documentation of approval or waiver of the study protocol approval has been obtained from the reviewing IRB/IEC and from all applicable regulatory authorities according to their requirements. A copy of the IRB/IEC approval letter will be filed in the study binder at the participating site. Any protocol amendments will be approved by the reviewing IRB/IEC before implementation.

### **7.2. Regulatory Documents**

Before the start of study testing, RMS must receive the following documents from each site:

- Curriculum vitae of the principal investigator
- Protocol Signature Page, signed and dated by the principal investigator
- Statement of investigator
- Financial Disclosure Form completed by the principal investigator and sub-investigators, if applicable
- IRB/IEC approval letter for the study protocol and consent form

### **7.3. Data Confidentiality and Privacy**

RMS and the site PI(s) will ensure study participant privacy/data confidentiality in accordance with applicable privacy and study conduct-related laws and regulations.

Under no circumstances shall any records sent to RMS or their authorized agents (such as a contract research organization) contain participant names, social security numbers, or other personally identifying information.

In case of a transfer of the records or copies thereof to another country, safeguards will be in place to adequately protect the participant's data. If during the conduct of this protocol, a breach of confidentiality is identified (e.g., when the data is not properly coded), this event will be reported to RMS, and may be reported IRB/ECs and/or regulatory/health authorities as applicable.

#### **7.4. Auditing Responsibilities**

RMS, its authorized agents, or authorities (regulatory or IRB) may perform audits during the course of the study or following study completion. Site personnel should contact RMS immediately if contacted with an audit request.

### **8. TRAINING**

#### **8.1. Study Monitor Training**

Each study monitor will be trained on **cobas® liat** CT/NG/MG and instrumentation, and will be qualified by training and experience to monitor the study.

#### **8.2. Operator Training and Qualification**

Each operator will be trained to perform the **cobas® liat** CT/NG/MG test. Operators will receive training during the site initiation visit (SIV), and will include protocol training, a video overview training of the **cobas® liat** CT/NG/MG test and instrument and a review of the instruction for use. Following the SIV training, operators will complete the 'add lot' procedure and capture the outcome of the procedure using the 'add lot' procedure form. Once the add lot procedure is complete, each site operator will perform a test run and capture the outcome of the test run using the operator form. This is done to document operator proficiency and understanding of the process and to ensure that the operator is able to successfully perform the testing. Operators will need to have successfully completed the 'add lot' procedure before performing sample testing for the study. Successful completion of this qualification activity will be reviewed by Roche study team clinical research associates and/or the study manager before the operators are authorized to perform sample testing. Documentation of training will be maintained in the study binder at the test site.

## 9. INVESTIGATIONAL PRODUCT AND SYSTEM DESCRIPTION

### 9.1. Reagents

The following items are for use on the **cobas® liat** CT/NG/MG:

- **cobas® liat** CT/NG/MG assay tubes
- **cobas® liat** CT, NG and MG control kit

### 9.2. System Description

The **cobas® liat** system automates and integrates sample preparation and purification, nucleic acid amplification, and detection of the target sequence in biological samples. Other than adding the sample to the assay tube (urine samples will first be transferred from a urine collection cup to a **cobas®** PCR media tube before getting transferred to the assay tubes), no reagent preparation or additional steps are required. The system is comprised of a **cobas® liat** analyzer with integrated software for running tests and analyzing the results, and a single-use disposable **cobas® liat** CT/NG/MG assay tube that holds all the sample purification and PCR reagents, and hosts the sample preparation and PCR processes.

After sample collection, the assay tube barcode is first scanned to identify the test and the sample barcode to link the sample ID with the assay run. The operator then transfers the sample into the **cobas® liat** CT/NG/MG assay tube using a transfer pipette. The operator then scans the assay tube barcode again before inserting the **cobas® liat** CT/NG/MG assay tube into the **cobas® liat** analyzer. The analyzer then automatically performs all of the nucleic acid test steps and reports results.

## 10. STUDY POPULATION

Participants with symptoms suggestive of an STI and/or known exposure to an STI presenting for care at settings not currently using POC PCR testing for STI pathogen (CT, NG, and MG) identification will be enrolled. To support the generalizability of results, we will target study sites that include participants in settings that reflect a range of cultural, economic, ethnic, and orientation diversity.

## 10.1. Inclusion Criteria

Participants will be required to meet all of the following criteria for enrollment:

- Sexually active people  $\geq 18$  years of age
- Willing and able to provide written, informed consent (according to the IRB at the respective sites)
- People seeking medical services for symptoms consistent with an STI and/or known exposure to an STI

Participants will be classified as symptomatic if they self-report one or more symptoms indicative of a potential urogenital infection from CT, NG, and MG, or based on the discretion of the examining clinician. The following list is based on common symptoms, but may not be an all-inclusive list:

- Lower genitourinary tract symptoms (eg, dysuria, urinary urgency/frequency, hematuria, abnormal vaginal bleeding) not more readily explained by another diagnosis
- Urogenital discharge (ie, urethral or vaginal)
- Lower abdominal or pelvic pain not more readily explained by another diagnosis (eg, kidney stones)
- Urogenital pain, or discomfort
- Testicular or scrotal swelling/tenderness
- Prostatic inflammation or tenderness
- Genital rash or lesion

## 10.2. Exclusion Criteria

Participants, regardless of symptom status, will be excluded from enrollment if any of the following criteria are met:

- Previously enrolled in the study

- Unable to provide informed consent
- Currently pregnant
- Declines POC testing
- Present for routine STI screening (asymptomatic)
- Use of antimicrobial agents active against CT, NG, or MG during the 21 days before sample collection. Examples of such antimicrobial agents include the following:
  - Macrolides (eg, azithromycin and erythromycin)
  - Penicillins (eg, amoxicillin)
  - Tetracyclines (eg, doxycycline)
  - Fluoroquinolones (eg., ciprofloxacin, ofloxacin, levofloxacin, and moxifloxacin)
  - Cephalosporins (eg, ceftriaxone and cefixime)
- Use of phenazopyridine-containing urinary pain relief medicines (ie, Azo or Pyridium) within 2 days prior to sample collection
- Use of any over-the-counter feminine hygiene products (internally or externally), such as vaginal moisturizers, lubricants (e.g., Replens, RepHresh, etc.), and feminine washes/vaginal douches, etc. within the 3 days prior to sample collection. The use of tampons or pads during menses is not an exclusionary criterion.
- Contraindication to vaginal swab sampling where vaginal swab sampling is the only option available
- Urination within 1 hour prior to sample collection (for subjects providing urine sample)

### 10.3. Informed Consent Process

Freely given informed consent, must be obtained (witnessed, where required by law or regulation) from participants prior to their enrollment in the study. Participants or their legally authorized representatives will be required to sign an IRB/IEC-approved informed consent form (ICF). The principal investigator(s) at each clinical site will ensure that:

- Each participant is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study.
- Each participant is notified that the participation in the study is voluntary and consent can be withdrawn at any time and for any reason.
- Each participant is given the opportunity to ask questions and allow time to consider the information provided.
- The original, signed ICFs are stored in the investigators study file and a copy of the signed ICF is given to the participants or to their legally authorized representative.
- Any incentives for participants who participate in the study as well as any provisions for participants harmed as a consequence of study participation are described in the EC/IRB approved ICF.

## **11. STUDY PROCEDURES**

Workflow is dependent upon whether urine or vaginal swab is the preferred diagnostic specimen. The preference of individual participants, clinicians, and/or clinics will be respected in this regard. Procedures below are described based on the sample selected for analysis: For male participants, urine will be the only sample utilized for all clinical sites. For female participants, clinics will have a choice of urine or vaginal swab. In clinical sites where only urine or only vaginal swab is the preferred sample, that alone will be provided. Sites that have no particular preference regarding the type of sample collected from female participants will be encouraged to take vaginal swabs but ultimately will be left to the discretion of the participant. All vaginal swabs at all sites will be self-collected.

### **11.1. Sample collection and testing workflow**

Participants upon entering the clinic, will be screened for the study ([Figure 2](#)). If the participant meets the criteria for study enrollment, subsequent to consent, the participant will provide either a urine sample or vaginal self-swabs depending on the sex assigned at birth, per participant and site's preference upon enrollment. As described in Section 6, EL-PCR testing will be performed for all participants irrespective of the sample type and study arm in which the participant is

assigned to. EL-PCR testing will include the use of the **cobas®** CT/NG Nucleic Acid Test for use on the **cobas®** 6800/8800 Systems and the **cobas®** TV/MG Nucleic Acid Test for use on the **cobas®** 6800/8800 Systems. The **cobas®** TV/MG Nucleic Acid Test for use on the **cobas®** 6800/8800 Systems will be configured to output only the MG results. For the purpose of determining sample collection options described below, sex assigned at birth will be considered, regardless of current gender identity.

**Urine sample:** Only one urine sample will be necessary to fulfill the SOC and study-related testing for enrolled participants where urine is the designated or preferred specimen. This single urine sample will be aliquoted by the operator into 3 parts: one for SOC testing (at the clinicians' discretion, sample #1), a second for POC testing (sample #2) conditional on the participant ultimately being assigned to the POC arm, and a final aliquot (sample #3) for EL-PCR testing.

**Vaginal sample:** When a vaginal swab is preferred, it will be self-collected in triplicate (3 swabs) and stored in 3 color-coded collection devices. The first swab will be banked for potential clinician-ordered SOC testing (sample #1), the second swab (sample #2) will be used for **cobas® liat** CT/NG/MG testing conditional on the participant ultimately being assigned to the POC arm, and the third swab (sample #3) will be sent for EL-PCR testing.

Sites will be provided a stack of envelopes containing randomized participant designations to either one of the 2 study arms. These envelopes will inform operators on how to process the samples and deliver information of, if appropriate, the POC test results. Upon enrollment of a participant, the operator will take the top-most envelope, in which information regarding the designation of the participant to specific arm is given. This information will be presented using one of the following messages:

1. THIS PARTICIPANT IS ASSIGNED TO THE STANDARD OF CARE ARM. No point-of-care STI results are available. Please proceed per your usual practice. As a reminder, please: (a) complete the patient management plan form, (b) discuss the management plan (including partner[s] management considerations) with the participant, and (c) return all completed paperwork to the study staff.

2. THIS PARTICIPANT IS ASSIGNED TO THE POINT OF CARE ARM. Point-of-care test results are enclosed. As a reminder, please: (a) complete the patient management plan form, (b) discuss the management plan (including partner[s] management considerations) with the participant, and (c) return all completed paperwork to the study staff.

Prior to execution of the study, operators will have received training in testing methods and instructions on how to process samples based on the contents of the envelopes.

Operators encountering message 1 will be instructed to bank sample #1 for SOC testing as determined by the clinician, to dispose of sample #2 immediately, and to send sample #3 for EL-PCR testing.

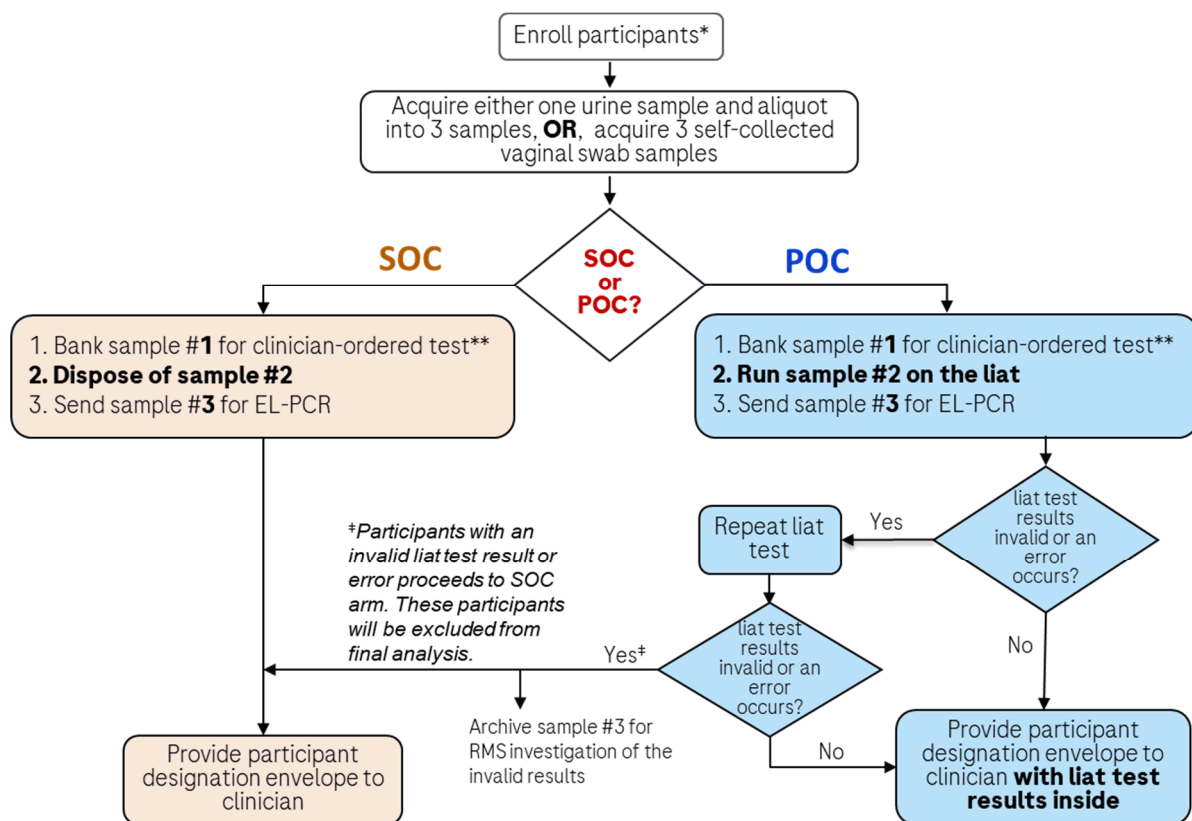
Operators encountering message 2 will be instructed to bank sample #1 for SOC testing as determined by the clinician, to run sample #2 on the **cobas® liat** CT/NG/MG POC test, and to send sample #3 for the EL-PCR testing. The **cobas® liat** CT/NG/MG test results will be recorded as ‘detected’, ‘not detected’, or ‘invalid’ for each pathogen. If the operator receives an error (ie, an aborted assay run by the system, running script, or user) or an invalid result from the **cobas® liat** CT/NG/MG POC test for any of the 3 pathogens, the operator will repeat the test ([Figure 2](#)). If the re-test results are ‘detected’ or ‘not detected’, the results will be reported to the clinician. If on the re-test, an error of one or more invalid results persist, the participant will be re-assigned to the SOC arm and the operator will be instructed to substitute the contents on the envelope with the SOC message:

THIS PARTICIPANT IS ASSIGNED TO THE STANDARD OF CARE ARM. No point-of-care STI results are available. Please proceed per your usual practice. As a reminder, please: (a) complete the patient management plan form, (b) discuss the management plan (including partner[s] management considerations) with the participant, and (c) return all completed paperwork to the study staff.

In this case, the operator will archive and ship sample #3 to RMS for further investigation on the cause of the invalid result or error. All data from participants with repeated invalid results or errors will be excluded from the final analysis.

On inclusion of the POC results as appropriate (ie, envelopes containing message 2 with valid results), all envelopes are sealed and delivered to the clinician either directly or by deposition at a designated area depending on the preference of the study site.

**Figure 2: Sample Collection and Testing Workflow**



\*Participant meets inclusion criteria and informed consent obtained

\*\*made at discretion of clinician

## 12. SPECIMEN HANDLING AND STORAGE

Specimens are human bodily fluids and therefore are capable of transmitting infectious diseases. Universal safety precautions should be used when handling, storing, processing, and disposing human bodily fluids.

Samples will be shipped to the test site in compliance with federal, state, and local regulations (eg, International Air Transportation Association [IATA], US Department of Transportation [US

DoT)) for shipment of diagnostic specimens. Upon arrival at the test site, samples should be stored according to the Manual of Operations.

The clinical sites will collect and aliquot samples as described in the procedure in Section 11.1. Once sample testing have been completed and EL-PCR results have been received, the samples can be discarded as per clinical site routine standard operating procedures.

For cases that receive invalid POC result or an error after repeat testing, sample #3 for the case will archived and shipped to RMS for further investigation on the cause of the invalid result.

### **13. REAGENT HANDLING AND STORAGE**

Each **cobas® liat** CT/NG/MG kit contains sufficient reagents to complete 20 tests. The kits must be stored according to instructions for use provided by RMS.

All kits should be handled as potentially hazardous materials. Safety Data Sheets describing kit contents; hazardous material identification and warnings; and proper storage, handling, and disposal of each component will be provided to each test site.

### **14. INVESTIGATIONAL PRODUCT ACCOUNTABILITY**

The principal investigator(s) must ensure that the investigational product(s) are used only for activities within the protocol scope. The investigational product should be supplied only to persons authorized to receive it. Upon completion or termination of the study or the principal investigator's part of this study, or at the request of RMS, the principal investigator shall return any remaining supply of the device or otherwise dispose of as directed by RMS. The study site must document receipt, use, and disposition of all investigational products received and used during the course of the study, as directed by RMS. Return of unused, expired, or malfunctioning product must be documented.

### **15. INTERPRETATION OF RESULTS**

For interpretation of test results, refer to instructions for use provided by RMS.

For detailed information on the interpretation of flags and comments, refer to the **cobas® liat** CT/NG/MG operator's manual.

Results (for runs and/or individual tests) may be deemed invalid by RMS for reasons including but not limited to the following:

- Protocol deviations (Section 20)
- Incidents (Section 21)
- Data generated during troubleshooting of the instrument system and/or assay

## 16. DATA COLLECTION, MONITORING, AND MANAGEMENT

### 16.1. Data Collection and Handling

Clinical study data will be collected on electronic Case Report Forms (eCRFs) and also in electronic files (test results) generated by the testing instrument(s).

The instrument printouts from the investigational device will serve as the source data and remain at the test sites. The electronic test results from the testing instruments serve as the actual raw data. The instrument printouts reflect the raw data files.

- eCRF data will be entered by the sites into a 21 Code of Federal Regulations (CFR) Part 11 compliant, electronic data capture (EDC) system. The site personnel will enter study data onto eCRFs, which will be monitored by the study monitors. Electronic consistency and logic checks will be used to verify the data. Unclear, incomplete, or inaccurate data will be queried for site clarification. eCRF data will be exported from the EDC system using a method described in a Data Transfer Specification (DTS). The exported eCRF data will be copied to a secure server and converted to statistical analysis software (SAS) data sets.
- All electronic test results transferred from the testing instruments are described in DTS, and will be copied to a secure server and converted to SAS data sets by RMS.

The principal investigator is responsible for the overall completeness and accuracy of the clinical study data.

## 16.2. Data Monitoring

RMS representative(s) will monitor the activities within the scope of this protocol in accordance with national regulations, GCP guidelines, and Roche procedures. The study site must maintain adequate records to fully document study conduct. The monitor(s) will review records to confirm that the data and documents are complete and accurate. RMS, its authorized agents, and appropriate regulatory/health authorities shall be granted direct access to all study-related documents to perform this verification.

The Principal Investigator(s) and relevant site personnel shall make every effort to be available during monitoring visits, audits, and inspections related to the diagnostic study.

## 16.3. Data Management and Quality Assurance

Data quality assurance will be performed according to established procedures applicable to EDC and industry regulations and guidance. Data review will be conducted during the study to ensure data quality and integrity before data-lock and transfer to RMS Biometrics. Electronic consistency checks will identify potential data errors at the time of data entry. Manual data review may also be performed. Unclear, incomplete, or illogical data will be queried for site clarification. The combination of electronic and manual data review will ensure data quality and integrity before the data are declared final and released to biostatistics for analysis.

## 17. STATISTICAL METHODOLOGY

### 17.1. Sample Size and Justification

Participants at increased risk of an STI may receive inappropriate treatment (either overtreatment [OT] or undertreatment [UT]) for STI(s) during their clinic visits. Observed proportions of inappropriate treatment for CT and/or NG of increased risk participants during their office visits can range from 20% to 50% in typical outpatient settings, as reported by various publications.<sup>28-</sup>

<sup>30</sup> In this same database, using POC STI testing has been shown to decrease the proportion of inappropriate treatment significantly. We define inappropriate treatment in both study arms as UT and/or OT on the day of the medical encounter based on CDC recommendations for the pathogen-specific results ultimately obtained by EL-PCR testing. The EL-PCR testing will be

conducted off-site using the Roche **cobas®** CT/NG and the Roche **cobas®** TV/MG tests; both are FDA-approved and validated PCR-based tests.

In the case of co-infections, inappropriate/appropriate treatments will be assessed independently for *each* pathogen.

In previous studies, the range of inappropriate SOC treatment of CT, NG or both ranged between 20% - 50%.<sup>28-31</sup> In this study, the proportion of inappropriate treatment is estimated to be 40% in the non-interventional arm or participants undergoing CDC STI guideline-recommended treatment (SOC) only. A minimum of 15% absolute reduction in the proportion of inappropriate treatment relative to the non-interventional (SOC) arm is expected. Based on these estimates, approximately 330 (156 in each arm) participants need to be enrolled. If we should account for a 5% dropout rate, 348 participants need to be randomized equally into each arm to demonstrate a 15% absolute reduction of inappropriate treatment from 40% to 25% with a given type I error of 2.5% (1-sided test) and a power of 80%.

## 17.2. Analyses for Study Objectives

All data analyses will be performed using SAS/STAT® software.<sup>31</sup>

### 17.2.1. Analyses for Primary Objectives

The primary objective of this study is to compare the clinical impact of timely results with POC STI testing for CT, NG, and MG on the **cobas® liat** system with the SOC on the proportion of inappropriate CT, NG, and MG treatments given to participants. The proportions of inappropriate treatment for participants will be calculated by comparing the frequency of inappropriate treatment (OT/UT) in the SOC arm as defined by comparison with EL-PCR vs inappropriate treatment (OT/UT) in the POC arm as defined by comparison with EL-PCR. These comparison will be made for the composite primary endpoints (CT, NG, and MG).

### 17.2.2. Analyses for Secondary Objectives

Additional analyses may be performed, including but not limited to comparing the degree of inappropriate treatment for the individual pathogens (MG, CT, NG) between the 2 arms,

clinician's confidence in the diagnoses and treatment recommendations, participants' satisfaction in the medical assessment and plan, and projections about costs and resource utilization.

### 17.2.3. Exploratory Analyses

At study mid-point, an assessment of the prevalence of all 3 pathogens will be checked, other study endpoints will be monitored as well. Enrollment and testing of at-risk participants will continue during this phase. Other exploratory analyses may be performed as needed.

## 18. NON-CONFORMING RESULTS

Non-conforming test results will be investigated for possible root cause by the study sponsor. To aid in this, operators will document which pathogens the POC test returned an invalid result and provide comment on possible cause for the invalid result. Additionally, sample #3 (as shown in [Figure 2](#)) will be archived and transferred to RMS for further investigation on possible cause of the invalid result. Rates of invalid results will be monitored throughout the trial.

## 19. ACCEPTANCE CRITERIA

The difference of inappropriate treatment for all 3 pathogens in the POC arm shall be minimum absolute reduction of 15% compared to the inappropriate treatment in the SOC arm. The acceptance criteria was derived from a combination of literature articles<sup>28,32</sup> describing similar study designs for rapid molecular testing and patient management, our internal biostatisticians, and an external Physician consultant that helped to justify clinical significance.

## 20. PROTOCOL DEVIATIONS

A protocol deviation is an unplanned excursion from or an instance of non-compliance with the protocol as written. The investigator is not allowed to deviate from the protocol, except when a deviation is necessary to protect the rights, safety, and well-being of the participant or the scientific integrity of the study. Each protocol deviation is to be reported to RMS on a separate protocol deviation eCRF. Protocol deviations may be reported to the IRB/EC and/or regulatory/health authorities as applicable. Each protocol deviation will be assessed for its

impact upon the data, which will be described in the final report. In case of repeated protocol deviations, documented corrective and preventive actions may be required.

## **21. INCIDENTS**

An incident occurs under circumstances such as instrument errors (eg, hardware failure or software error), external power failure, problems with reagents, or sample QNS (quantity not sufficient). Each incident is to be reported to RMS on a separate Incident Report eCRF. RMS will determine whether an incident affects the validity of the study data.

### **21.1. Device Deficiencies**

Device deficiencies (DD) are classified as incidents related to the inadequacy of an investigational medical device in respect to its identity, quality, durability, reliability, safety or performance, which includes malfunctions, use errors and/or inadequate labeling. A DD is a device-related incident where an adverse event (AE) has not occurred in association with the device.

## **22. ADVERSE EVENT REPORTING AND MANAGEMENT**

### **22.1. Definitions**

Safety event definitions under applicable standards are listed below:

| Term                               | Definition from ISO 20916: 2019                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Adverse Event (AE)</b>          | <p>Any untoward medical occurrence, inappropriate patient management decision, unintended disease or injury, or untoward clinical signs, in subjects, users, or other persons, with any connection to study related activities, whether or not related to the IVD medical device under investigation</p> <p><i>Note 1: Adverse events can be caused by, for instance, insufficient or inadequate instructions for use, deployment, installation, operation, or any malfunction of the IVD medical device under investigation.</i></p> <p><i>Note 2: This definition includes the malfunction or deterioration of a device which has not yet caused death or serious injury, but which could lead to death or serious injury.</i></p> <p><i>Note 3: This definition is not intended to be used in determining whether an event is reportable to a regulatory authority.</i></p> <p><i>Note 4: For users or other persons, this definition is restricted to events related to investigational (IVD) medical devices.</i></p> <p><i>Note 5: False negative or false positive results are not considered an adverse event unless in an interventional study, inappropriate patient management decisions are made based on those false results.</i></p> |
| <b>Adverse Device Effect (ADE)</b> | <p>An Adverse Device Effect (ADE) is an adverse event related to the use of an IVD medical device under investigation.</p> <p><i>Note 1: This definition includes any adverse event resulting from insufficient or inadequate instructions for use, installation, operation, or any malfunction of the IVD medical device under investigation.</i></p> <p><i>Note 2: This definition includes any event resulting from use error or from intentional misuse of the IVD medical device under investigation.</i></p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| <b>Serious Adverse Event (SAE)</b> | <p>A Serious Adverse Event (SAE) is an AE that led to any of the following:</p> <ul style="list-style-type: none"> <li>(a) death</li> <li>(b) serious deterioration in the health of the subject, users or other persons as defined by one or more of the following: <ul style="list-style-type: none"> <li>(i) a life-threatening illness or injury, or</li> <li>(ii) a permanent impairment of a body structure or a body function including chronic diseases, or</li> <li>(iii) in-patient or prolonged hospitalization, or</li> <li>(iv) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function</li> </ul> </li> <li>(c) fetal distress, fetal death, or a congenital abnormality or birth defect including physical or mental impairment</li> </ul> <p><i>Note 1: Planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigation plan, without serious deterioration in health, is not considered a serious adverse event.</i></p>                                                                                                                                                                        |

| Term                                                 | Definition from ISO 20916: 2019                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Serious Adverse Device Effect (SADE)</b>          | An SADE is an ADE that has resulted in any of the consequences characteristic of a serious adverse event (SAE)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| <b>Anticipated Serious Adverse Device Effect</b>     | An Anticipated Serious Adverse Device Effect is an SADE which by its nature, incidence, severity or outcome has been identified in the current version of the risk analysis report.<br><br><i>Note 1: Anticipated serious adverse device effects can also be described in the study protocol, investigator brochure, and subject informed consent, when applicable.</i>                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| <b>Unanticipated (Serious) Adverse Device Effect</b> | An Unanticipated Serious Adverse Device Effect (USADE) is an SADE which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.<br>Additional Definition from Code of Federal Regulations (CFR § 812.3(s))<br>Unanticipated Adverse Device Effect (UADE) means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. |
| <b>Device Deficiency (DD)</b>                        | Device deficiency is inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety or performance<br><br><i>Note 1: Device deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labeling.</i><br><i>Note 2: This definition includes device deficiencies related to the investigational medical device or the comparator.</i>                                                                                                                                                                                                                                                                                                                                                       |
| <b>Incident</b>                                      | Not defined                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| <b>Serious Incident</b>                              | Not defined                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |

## 22.2. Assessment and Categorization of Safety Related Events

The sponsor and the investigator(s) will assess the relationship of an (S)AE to the IVD device under investigation, the comparator (if applicable), and the study procedures involved. In general, the assessment will be based on clinical judgment, relevant study documents, and the presence of confounding factors (e.g. concomitant medication/treatments, the natural history of the underlying disease, other concurrent illness or risk factors).

(S)AEs will be categorized according to 4 different levels of causality –

1. Not related: Relationship to the device, comparator (if applicable), or procedures can be excluded
2. Possible: The relationship with the use of the investigational device or comparator (if applicable), or the relationship with procedures, is weak but cannot be ruled out completely. Alternative causes are also possible. Instances where relatedness cannot be assessed, or no information has been obtained should also be classified as possible.
3. Probable: The relationship with the use of the investigational device or comparator (if applicable), or the relationship with procedures, seems relevant and/or the event cannot be reasonably explained by another cause.
4. Causal Relationship: The (S)AE is associated with the investigational device, comparator (if applicable) or with procedures beyond reasonable doubt.

### **22.3. Recording and Reporting**

Recording and reporting of (S)AEs and DDs that occur during this study will be performed in accordance with applicable regulations.

#### **22.3.1. Investigator Responsibilities**

The investigator(s) must record clinical utility study-related safety events occurring at their site(s) using the appropriate AE/SAE case report form provided by RMS.

AEs and/or DD shall be reported to RMS in a timely manner. The investigator(s) must report occurrences of the following types to RMS within approximately 24 hours of becoming aware of the occurrence:

1. SAEs or SADEs affecting study participants or associated with study procedures e.g. sample collection procedures for the clinical utility study;
2. DDs that might have led to an SAE or SADE under less fortunate circumstances or if appropriate action had not been taken;
3. DDs that might have led to patient mismanagement (e.g., a clinician may elect to omit antimicrobial treatment based on a potentially false-negative result).

In alignment with the RMS the investigator(s) should also ensure that the event is reported to their reviewing IRB(s)/EC(s).

### **22.3.2. Sponsor Responsibilities**

RMS will assess all AEs and DD for their seriousness and their relationship to the IVD device under investigation, the comparator (if applicable), and the study procedures involved such as sample collection procedures for the clinical utility study.

If the assessments confirm reportability of events, then RMS will ensure respective reporting to IRB(s)/EC(s) and other competent authorities as required. In case of disagreement between the RMS and the principal investigator(s), RMS shall communicate both assessments to concerned parties. If applicable, this information will also be sent to all participating principal investigator(s) within the required timeframes. The reviewing IRB(s)/EC(s) and other competent authorities will be informed of significant new information about the clinical IVD investigation as required by those bodies.

### **22.3.3. Incidents Associated With an On-Market IVD**

Any deficiencies encountered during the conduct of the protocol related to the identity, quality, durability, reliability, safety, effectiveness, or performance of an on-market IVD or medical device that is being used according to its approved intended use should be reported to the Roche study team.

Incidents associated with on-market devices must adhere to IRB/EC reporting requirements and all applicable regulations and health authorities.

### **22.3.4. Roche Molecular Systems Contact for Safety Reporting**

██████████ MBA  
Roche Molecular Systems, Inc.  
4300 Hacienda Drive  
Pleasanton, CA 94588  
Cell phone: ██████████  
Fax: ██████████  
E-mail: ██████████

### **22.4. Scope of Safety Events**

Prospectively collected samples are required as part of this clinical utility study. AEs associated with sample collection include events related to study procedures for the IVD utility study, e.g.

collection of study specimens or events associated with study participants that have been impacted by an incorrect investigational device result and concomitant patient management decisions. Additional information on impact of an incorrect result is described in Section 23.1.

## **23. BENEFITS AND RISKS OF THE INVESTIGATIONAL IVD DEVICE IN THE CLINICAL UTILITY STUDY**

### **23.1. Assessment of Risk**

This is a significant risk study. The investigational **cobas® liat** CT/NG/MG test results may potentially be used for participant care as deemed appropriate by the clinician including their decisions to prescribe or not to prescribe antibiotics. It is conceivable that a false-negative or false-positive result could occur with the POC test that could adversely influence clinician treatment decisions. As with any currently approved POC diagnostic tests, there is potential for discordance with the results of an SOC test for the same analytes. The primary action taken for risk mitigation is to confirm the results of the POC test using an FDA-approved SOC test (ie, EL-PCR). Two particular discrepancies are possible – false negatives and false positives. For the purposes of this study, false-negative - the POC test is negative for one or more pathogens while the EL-PCR test is positive for those same pathogens, and false-positive - when the POC test is positive for one or more pathogens while the EL-PCR test is negative for those same pathogens. The impact of the occurrence of false results are:

*POC test reports a false-negative.* In this scenario, clinicians may elect to omit antimicrobial treatment based on the results of the POC test when in fact the participant is positive (ie, the EL-PCR test result is positive) for one or more pathogens. On recognition of the existence of the false-negative, the clinician will be immediately informed at which time the clinician may elect to change the treatment. A false-negative result could lead to a participant not being treated appropriately resulting in a delay in treatment (for participants and partners), potential disease progression, and potential spread to contacts. As the confirmatory result (EL-PCR) should become available in the same time frame as that of current standard of care,

correct treatment would not be delayed any more than it is currently delayed in the SOC arm.

In addition, clinicians could potentially become over-reliant on the POC results (a case that would not happen in the SOC arm) and as a result, prematurely truncate their clinical decision process. To mitigate this risk, during training, it will be emphasized to clinicians that the POC is not to be used as a substitute for thorough and sound clinical judgment but only to help guide their treatment plan. Moreover, experience dictates clinicians do not necessarily act on negative POC results alone when they are aware that their patients are high-risk (eg, contact based on a known pathogen) and are likely to prescribe presumptively based on their own or patient preference. Furthermore, this is in line with the 2021 CDC sexually transmitted diseases (STD) Guidance recommendations for presumptive treatments.

*POC test reports a false-positive.* False-positive POC testing would potentially lead to unnecessary STI treatment, the risk of which is recognized to be sufficiently low given that the CDC has previously consistently recommended presumptive treatment prior to confirmation of most cases for patients identified as sufficiently high-risk (eg, contact with the known pathogen). Unnecessary antibiotic exposure is an inherent risk to all patients seeking treatment for potential STIs, not just those being tested by POC; it is expected to be an even greater risk to participants in the SOC arm given that clinicians have no access to POC tests to guide their treatment decisions and literature supports routine over-prescription of antimicrobials.<sup>33</sup>

The incorporation of the EL-PCR into the study is designed to minimize risk by confirming the results of the **cobas® liat** CT/NG/MG POC test using an FDA-approved and validated test. Testing of the EL-PCR will be performed by a CLIA-certified reference laboratory. The results of this external confirmatory test will be delivered to clinicians in the POC arm only. In an event of a discrepant POC:EL-PCR result, clinicians will be immediately contacted and notified of the discrepancy. At this time, if clinicians in the POC arm had elected to order their usual SOC test, they will be encouraged to compare the results of that test with the POC and EL-PCR test. They will also be reminded that the POC test is an experimental intervention and the external EL-PCR

is a validated standard care test to help guide them in their treatment decisions. [Table 1](#) summarizes actions to be taken in the case of discrepant results between the POC and EL-PCR.

**Table 1: Risk Mitigation Action Plan for Discordant Test Results in POC Arm**

|         | Clinician | SOC test | POC test | Tx Plan | External PCR*<br>(study purpose) | Guidance                                                                                                                                    |
|---------|-----------|----------|----------|---------|----------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|
| SOC-arm | 1         | X        |          | A       | X                                |                                                                                                                                             |
|         | 2         |          |          | B       | X                                |                                                                                                                                             |
| POC-arm | 3         | X        | X        | C       | X                                | SOC=POC → no guidance<br>SOC:POC discordant → provide External PCR result                                                                   |
|         | 4         |          | X        | D       | X                                | POC=External PCR → no guidance<br>POC:External PCR discordant → provide External PCR results → revise Tx decision at clinician's discretion |

\*only given to clinician in case of discordant test results.

PCR: polymerase chain reaction, POC: point of care, SOC: standard of care, Tx: treatment, X: test conducted.

## 23.2. Residual Risks Associated With the Clinical Study

Collection of urine and vaginal samples is considered part of the standard clinical practice for the testing of CT, NG, and MG. Samples will be obtained using a medically routine sampling procedure. There is a remote probability of injury from either standard of collection of urine or vaginal swab (self-collected). Overall, the risks are considered medically acceptable. Any potential risks associated with the sample collection procedure will be indicated in the study's ICF.

The risk to operators performing the POC test is minimal, but are described here to document its possibility during the conduct of the trial. Potential risks to personnel at the testing sites include contact with hazardous materials and injury to the operator of a **cobas® liat** instrument.

One residual chemical hazard, which may impact laboratory technicians (operators), is irritation / inflammation caused by a leaking **cobas® liat** CT/NG/MG assay tube. Although unlikely, a leaking assay tube might expose the user to a potential chemical hazard. The recommended control measure for this hazard is use of adequate Personal Protective Equipment (PPE).

A biological hazard that may impact the operator is the potential risk of infection when handling infectious material. The recommended mitigations include: 1) devices are to be handled according to biohazard precautions, 2) all regulations are to be applied to determine the safe disposal, and 3) proper training, and monitoring visits to ensure protocol adherence.

Incorrectly operating the **cobas® liat** analyzer could result in a wasted **cobas® liat** CT/NG/MG assay tube and thus using up additional sample. The harm of this risk would be the POC test results being delayed which potentially impacts clinical decision making and patient care. Our effort to mitigate this risk would be to provide operator and clinical sites with Instructions for Use and Quick Reference Guides for the analyzer and assay operation.

### **23.3. Minimization of Risks**

Clinical protocols are submitted to the IRB prior to start to ensure that participants are not subject to undue risk. The procedures set forth in Sections 12 and 13 will help mitigate operator risk and exposure that can potentially occur during the execution of the study. To minimize the risk of false results from the **cobas® liat** CT/NG/MG, if any, the device has been analytically validated and appropriate controls are included.

### **23.4. Potential Benefits of the Investigational IVD and Clinical Study**

A potential benefit of the clinical investigation is that validation of the investigational assay may improve the ability of clinicians to direct participants to appropriate diagnosis.

### **23.5. Risk Benefit Assessment**

Given the unmet medical need for rapid and simultaneous POC detection and differentiation between CT, NG, and MG in easy-to-collect urogenital specimens (both urine and vaginal swabs) from symptomatic and asymptomatic individuals and the benefits and risks stated above,

RMS concludes that the medical value and public health benefit outweigh the potential risks of the study.

## **24. STUDY QUALITY ASSURANCE**

RMS will monitor the study in accordance with federal regulations, ICH guidelines, and RMS standard operating procedures.

RMS or regulatory authorities may perform audits during the course of the study or following study completion. Site personnel should contact RMS immediately if contacted with an audit request.

## **25. ESTIMATED DURATION OF STUDY**

This study aims to enroll approximately 348 participants split equally between the 2 study arms from 3 geographical enrollment sites across the US. Based on an enrollment rate of 30 participants per month per site from the historical data, the study duration is expected to be approximately 3-4 months from the start of participant enrollment.

## **26. RECORD RETENTION**

Study testing will be considered complete when RMS has copies of the following items on file from each participating site:

- All test result printouts
- All completed eCRFs
- All resolved queries
- All exported test results

PI(s) must maintain all study records as stipulated by RMS in accordance with applicable regulations and the date specified in the clinical study agreement.

Before destroying any study records, the PI(s) must contact RMS for permission, even if the records retention period has passed. If the PI(s) are unable to maintain the study records as

required above, they must contact RMS to make arrangements for the appropriate records transfer.

## **27. REVISIONS TO THE PROTOCOL**

Modifications to the protocol will be submitted for further review in accordance with regulatory requirements that govern conduct of the study.

If a change to this protocol is required, that would affect the design or conduct of the study, the appropriate changes may be made via a protocol amendment. The protocol amendment will be subject to the same standard procedures as the initial version of the protocol or the current applicable standard procedures.

Any protocol amendments will be approved by the reviewing IRB/IEC before implementation. All participating principal investigators must provide the sponsor with a signed Protocol Signature page for all amendments unless their involvement is complete at the time of the amendment.

Changes that do not affect the safety, scope, and scientific quality of the study may be implemented via an administrative memo provided to the study sites and reviewing IRB/EC and filed in the eTMF. The memos are effective immediately. All of these changes will be incorporated into future amendments.

Where applicable, major changes may be reportable to applicable national health authorities.

Waivers permitting deviations from the study protocol are not permitted.

## **28. EARLY TERMINATION OF THE STUDY**

Temporary suspension or premature termination of this study may occur at the discretion of RMS, or an opinion change by the reviewing IRB/EC. If this study is prematurely terminated or discontinued, RMS will promptly notify the principal investigator(s), IRB/EC, and health authorities, as applicable. Study activities may resume once concerns about safety, protocol compliance, and data quality are addressed and satisfy RMS, IRB and/or regulatory authorities.

As directed by RMS, study materials must be collected, and study data must be completed to the maximum extent possible.

If the study is temporarily suspended, the study may resume once causal concerns for suspension about safety, protocol compliance, and data quality, if any, are addressed to the satisfaction of the sponsor, IRB and/or regulatory authorities. Regardless of the outcome, RMS will document protocol activities and circumstances surrounding early termination.

The Principal Investigator(s) shall notify RMS in advance if withdrawal from the study is planned for any reason. If an investigator withdraws suddenly due to unforeseen circumstances, RMS must be notified as soon as possible. In the event of withdrawal, study records must be transferred to RMS or to an acceptance designee, such as another study investigator or institution.

## **29. USE OF STUDY FINDINGS**

The principal investigator is obligated to provide RMS or its designee with complete test results and all data obtained in this study. Only RMS may make information obtained during this study available to other investigators and third parties, including regulatory agencies.

## **30. PUBLICATION POLICY**

Data obtained from this study are considered confidential and will be used to support market approval of the **cobas® liat** CT/NG/MG by RMS. The principal investigators may not individually publish the study results. If a principal investigator is interested in a joint publication or presentation of the study results, the manuscript, presentation, and/or abstract must be provided to RMS in accordance with the executed contract, or, if not stated in the contract, at least 30 days before the expected date of submission to the intended publisher or planned presentation. As applicable, the publication of results shall be carried out in accordance with legal requirements and recognized ethical principles.

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## Appendix 1. Patient Management Plan (PMP)

See Attachment

## Appendix 2. Patient Questionnaire – Point of Care Version

See Attachment

## Appendix 3. Patient Questionnaire – Standard of Care Version

See Attachment

## Appendix 4. Clinician Satisfaction with Diagnostic Test Questionnaire (CSDT-Q)

See Attachment