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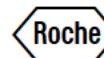
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Abbreviations and Definitions of Terms

Term	Description
CDC	Centers for Disease Control and Prevention
cobas® liat CT/NG/MG	cobas® liat CT/NG/MG nucleic acid test
CSDT-Q	Clinician Satisfaction with Diagnostic Test Questionnaire
CT	<i>Chlamydia trachomatis</i>
EL-PCR	external laboratory-polymerase chain reaction
FDA	US Food and Drug Administration
IRB	Institutional Review Board
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 ' cobas® liat CT/NG/MG nucleic acid test'
RMS	Roche Molecular Systems, Inc.
SAS	statistical analysis software
SOC	standard of care
STI	sexually transmitted infection
UT	undertreatment
US	United States

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1 INTRODUCTION

This statistical analysis plan (SAP) describes the planned analyses for study RD006770 based on the amended version of the study protocol dated 12-MAR-2024. It summarizes the study design and endpoints and describes the detailed statistical methodology to be used for the analyses.

If any amendment to the study protocol impacts the planned analyses or study population(s), this SAP will be updated accordingly.

2 STUDY OBJECTIVES

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)¹ 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;

¹ 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.

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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.

3 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)

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In both arms, the clinician will see and evaluate the participant and will complete a standardized form, known as a patient management plan (PMP) , 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.

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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 or Patient Questionnaire – Standard of Care Version, based on the participant's assigned study arm. The versions differ only in their instructions which describe the test being evaluated.

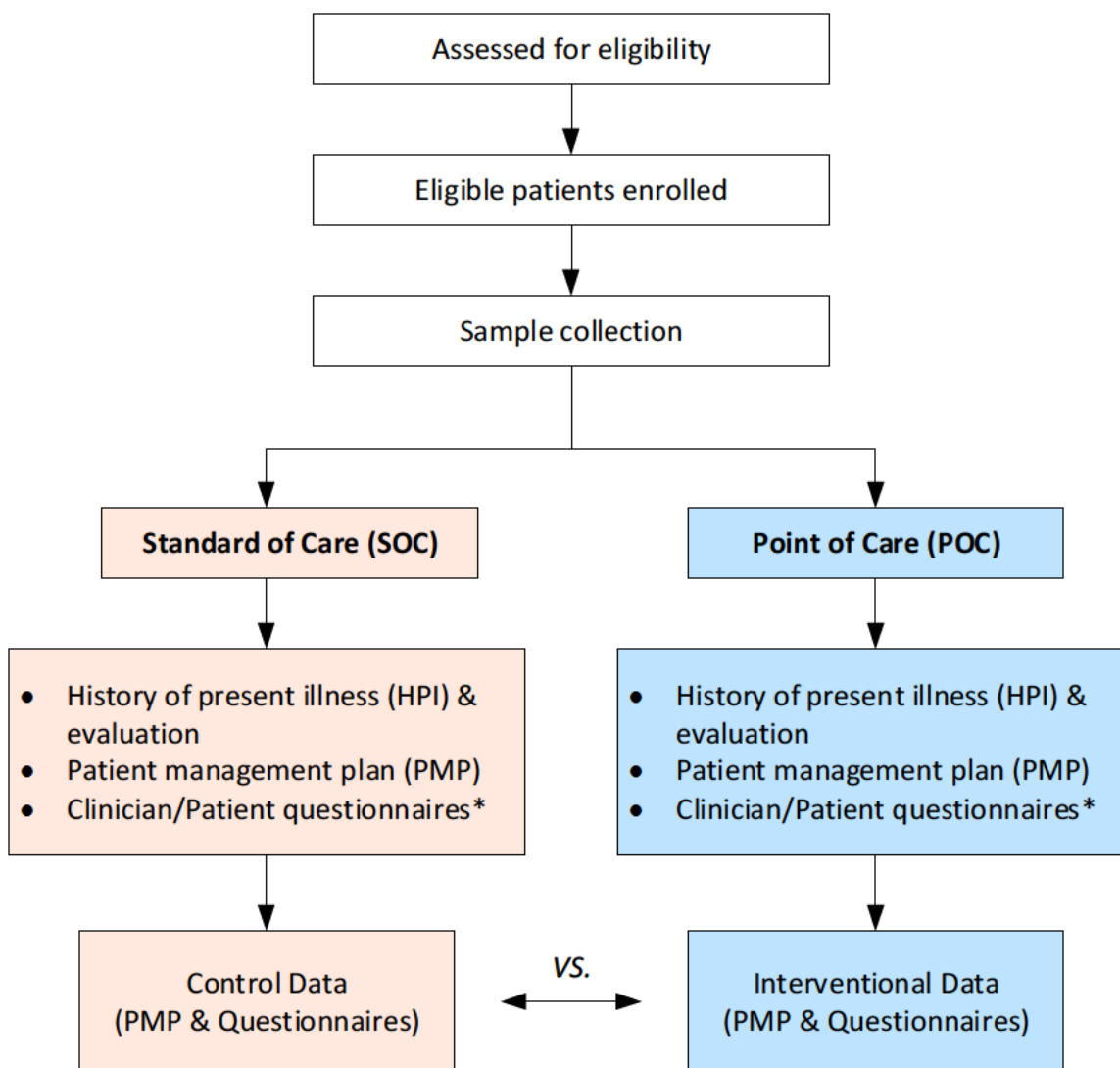
All clinicians involved in the study will complete a clinician questionnaire, the Clinician Satisfaction with Diagnostic Test Questionnaire (CSDT-Q), which assesses satisfaction with the diagnostic test (**cobas[®] liat** CT/NG/MG) compared with standard care. For this study, 'clinician' refers to any 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.

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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.



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4 SAMPLE SIZE DETERMINATION

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.²⁸⁻

³⁰ 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%.²⁻⁵ 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%.

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5 ANALYSIS POPULATIONS

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.

5.1 Inclusion Criteria

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

Sexually active people ≥ 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 (e.g., dysuria, urinary urgency/frequency, hematuria, abnormal vaginal bleeding) not more readily explained by another diagnosis
- Urogenital discharge (i.e., urethral or vaginal)

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- Lower abdominal or pelvic pain not more readily explained by another diagnosis (e.g., kidney stones)
- Urogenital pain, or discomfort
- Testicular or scrotal swelling/tenderness
- Prostatic inflammation or tenderness
- Genital rash or lesion

5.2 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)

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- 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)

6 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.



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6.1 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 3, 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.

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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

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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:

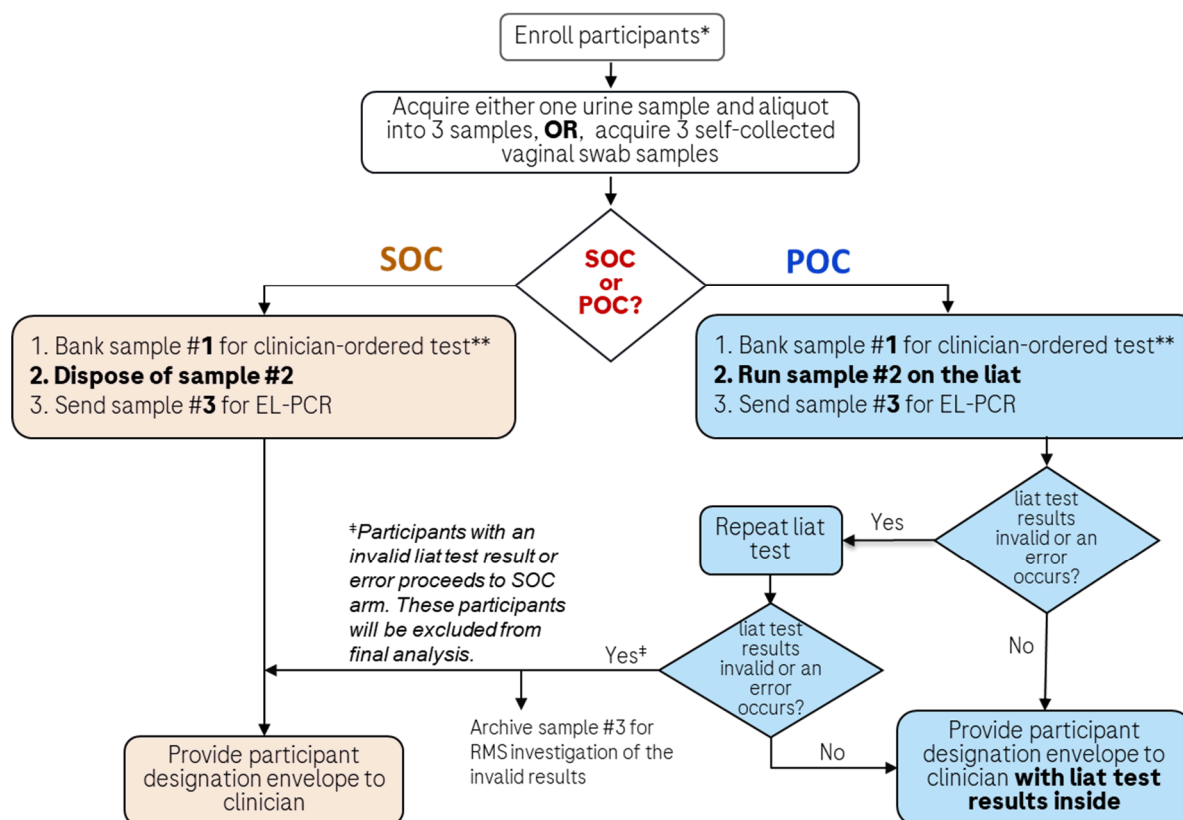
THIS PARTICIPANT IS ASSIGNED TO THE STANDARD OF CARE ARM. No point-of-care STI results are available. Please proceed per your usual practice. As a reminder, please: (a) complete the patient management plan form, (b) discuss the management plan (including partner[s] management considerations) with the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

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Figure 2: Sample Collection and Testing Workflow



*Participant meets inclusion criteria and informed consent obtained

**made at discretion of clinician

7 ANALYSIS POPULATIONS

7.1 Enrolled population

Subjects meeting the inclusion and not meeting the exclusion criteria described in the study protocol who have signed the informed consent are deemed enrolled for the study.

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7.2 Evaluable population

Enrolled subjects with a valid result for each of the 3 pathogens by EL PCR are considered evaluable and included in the analysis of the primary and secondary endpoints. All analysis will be performed overall and by arm using only the evaluable population.

8 GENERAL ANALYSIS COMMENTS

Patient characteristics will be summarized and described using appropriate descriptive statistics. Continuous variables will be described using the mean and standard deviation (SD), median and inter-quartile range, and Range.

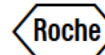
Categorical variables will be summarized using frequencies and proportions. Differences across arms will be assessed using the chi – squared test and students t – test for categorical and normally distributed continuous variables. For skewed variables, the Wilcoxon sum – rank test will be used.

The association between treatment and binary outcomes will be assessed using contingency tables. Relative Risk (RR) and its 95% confidence interval will be estimated using the PROC FREQ procedure in SAS with the RISKDIFF and RELRISK options on the TABLES statement. The Number Needed to Treat (NNT) will be calculated as the reciprocal of the absolute risk difference, derived from the same procedure.

P values less than 5% will be considered statistically significant. All data analyses will be performed using SAS/STAT® software.⁶

As part of data validation, a line listing of each enrolled subject will be created and reviewed by two independent study team members for validity of classification of participants into their respective endpoints. Resolution in discordant opinions will be done by the entire study team.

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9 STATISTICAL METHODS

9.1 Determination of Inappropriate treatment and Appropriate Treatment

A breakdown of treatment outcomes as well as patient status is shown in tables 1 and 2 below:

Table 1: EL PCR test results / Treatment (Rx) / Treatment (Tx) Outcomes

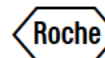
EL PCR results	Rx	Tx Outcomes	UT or OT
+		Appropriate	
+		Inappropriate	UT
+		Inappropriate	UT
-		Inappropriate	OT
-		Inappropriate	OT
-		Appropriate	

Note: Pathogen-specific CDC Rx: Correct ; Incorrect ; None = blank

Table 2: Patient / Results / Treatment (Rx) / Treatment (Tx) Outcomes

Patient	CT	Rx	NG	Rx	MG	Rx	Tx Outcomes	OT or UT
A	+		-		-		Appropriate	
B	+		-		-		Inappropriate	OT
C	+		+		-		Appropriate	
D	+		+		-		Inappropriate	UT

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E		+			+			-			Inappropriate	UT
F		-			+			-			Inappropriate	OT
G		-			+			+			Appropriate	
H		-			+			+			Inappropriate	UT
I		-			+			+			Inappropriate	OT/UT

Note: Pathogen-specific CDC Rx: Correct ; Incorrect ; None = blank
Results: +/- ; Undertreatment (UT) / Overtreatment (OT)

9.2 Description of Analysis

9.2.1 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. This comparison will be made for the composite primary endpoints (CT, NG, and MG).

9.3 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,

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

9.4 Exploratory Analyses

At study mid-point where enrollment numbers exceed 50%, an assessment of the prevalence of all 3 pathogens will be assessed as well as other study endpoints.

Appropriate and inappropriate treatments will be computed for the composite endpoint as well as individual pathogens.

Enrollment and testing of at-risk participants will continue during this phase. Other exploratory analyses may be performed as needed.

10 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^{28,32} 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.

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12 ATTACHMENTS

N/A.

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