1. Project summary

a. Background information and rationale
In 2012 WHO estimated that approximately 357 million people aged 15 to 49 are infected each year with four curable sexually transmitted infections (STIs), chlamydia, gonorrhoea, syphilis, and trichomoniasis. Men who have sex with men (MSM) bear a high burden in HIV and STIs. Chlamydial infection is caused by the obligate intracellular pathogen, *Chlamydia trachomatis* (Ct) and gonococcal infection is caused by the bacteria *Neisseria gonorrhoeae* (Ng). The diagnostic tests of choice for these infections are NAATs. However, NAATs are technically demanding and not widely available in most healthcare settings in developing countries. MSM may not present to clinics when they are symptomatic because they are marginalised from the healthcare system. Moreover, these STIs are often asymptomatic. Undetected infection can result in serious long-term complications and increased risk of HIV acquisition and transmission. Screening and appropriate treatment for infections in asymptomatic individuals can reduce the risk of developing serious long-term complications, interrupt onward transmission to sexual partners and possibly the exchange of genetic elements between commensal and pathogenic Neisseria species that confer antimicrobial resistance.

b. Study hypothesis and objectives
The overall objective of the World Health Organization (WHO) Point-Of-Care (POC) Diagnostics Evaluation Scheme for Sexually Transmitted Infections (STI) is to provide advice to WHO Member States and other relevant public health institutions on the performance and operational characteristics of commercially available STI diagnostic tests that can be used at the point-of-care (hereafter referred to as POCTs). The specific objectives of this clinic-based evaluation of POCTs for the screening of asymptomatic genital, anorectal and pharyngeal chlamydial and gonococcal infections, as recommended by the WHO guideline for HIV and STI prevention and treatment, in MSM are to determine the performance of POCTs for the screening of genital, anorectal and pharyngeal chlamydial and gonococcal infections in MSM compared to that of nucleic acid amplified tests (NAATs) as a reference standard and to assess the operational characteristics and acceptability of these POCTs to patients and healthcare providers.

c. Study methods
Consecutive MSM presenting to the clinic at the evaluation sites or outreach settings and who fit the inclusion criteria will be asked to participate in the study. Patients will be informed by the healthcare provider and the consent form. The sample size calculation depends on the estimated performance of the POCT compared to the reference standard and the prevalence of infection at the study site. For example, if it is estimated that the sensitivity of a new test is 80% compared to the reference standard, then 200 infected study subjects by the reference standard test would need to be recruited for a confidence interval of ±5% around the point estimates of sensitivity and specificity. If the prevalence of infection in the study population is 10%, then there will be 10
infected subjects per 100 patients seen at the clinic. Then 2,000 (100/10 x 200) patients will need to be recruited.

Three types of specimens will be collected: Urine, 2 oropharyngeal swabs taken simultaneously and 2 anorectal swabs taken simultaneously. Swabs for the reference test should be transported to the laboratory in accordance with standard operating procedures at the clinic. The reference or "gold standard" test for this evaluation is a NAAT which should be performed on a urine sample and each of the oropharyngeal or anorectal swabs.

Staff performing the evaluation should be qualified and competent to undertake the task and demonstrate that they can perform the test properly through proficiency testing programme results. There should be a regular independent assessment of the laboratory quality assurance and quality control procedures, and of the proficiency of the laboratory to do the reference tests for evaluation, and whether the evaluations are conducted in compliance with the Principles of Good Clinical Practice (GCP) and Good Clinical Laboratory Practice (GCLP). Data from the evaluation will be entered into a standardised spreadsheet for analyses. Double entry reduces chances of error. A positive case is defined as a patient with a positive reference standard test result regardless of specimen type. The sensitivity, specificity, positive and negative predictive values for each POCT will be calculated by comparing the POCT results to the validated reference test results.

A clinic-based evaluation is used to determine test performance when the test is performed by clinic personnel who are not trained laboratory technicians. It is also important to assess operational characteristics of these POCTs such as the ease of use, acceptability of the tests to patients and clinic personnel at POC testing sites.

2. Detailed description of the project

2.1 Background information and rationale

In 2012 WHO estimated that approximately 357 million people aged 15 to 49 are infected each year with four curable sexually transmitted infections (STIs), chlamydia, gonorrhea, syphilis, and trichomoniasis. MSM bear a high burden in HIV and STIs. MSM in low and middle-income countries (LMIC) have an on average 19.3 times higher chance of being infected with HIV compared to the general population. In high-income countries, among new HIV cases, the proportion attributed to male–male sex has increased in recent years. Syphilis has been identified as a growing problem among MSM in all world regions. In Europe, 48% of all new syphilis cases and 38% of all gonorrhoea cases in 2012 were reported among MSM. The EMIS study across Europe showed that 14.5% of MSM self-reported a history of gonorrhoea, 8.6% of syphilis and 8.1% of chlamydial infection. In LMIC the prevalence rates of chlamydial and gonococcal infections in MSM reached up to 14.9% and 16.1% respectively. In Australia, MSM, with a prevalence of rectal chlamydial infection of 5.6%, are amongst the populations with the greatest burden. There are also indications that MSM are one of the core groups that are key to the emergence, onward transmission and outbreaks of antimicrobial-resistant gonococcal infection. Chlamydial infection is caused by the obligate intracellular pathogen, *Chlamydia trachomatis* (Ct) and gonococcal infection is caused by the bacteria *Neisseria gonorrhoeae* (Ng).

The diagnostic tests of choice for these infections are NAATs. However, NAATs are technically demanding and not widely available in most healthcare settings in developing countries. Simple rapid POCTs for the diagnosis and screening of these infections are commercially available, but there is limited data on their performance and utility.

The evaluation of these POCTs is important for two reasons. Key populations are at high risk of acquiring and transmitting STIs, but they may not present to clinics when they are symptomatic because they are marginalised from the healthcare system. Moreover, these STIs are often asymptomatic. Undetected infection can result in serious long-term complications and increased risk of HIV acquisition and transmission. Screening and appropriate treatment for infections in asymptomatic individuals can reduce the risk of developing serious long-term complications, interrupt onward transmission to sexual partners and possibly the exchange of genetic elements between commensal and pathogenic *Neisseria* species that confer antimicrobial resistance. Screening MSM for these curable STIs at non-traditional or outreach settings is a high priority as recommended in the WHO Guideline for MSM/Transgender People in 2011. Evaluating the performance of these tests and their acceptability to patients and health are high priorities for WHO.
A clinic-based evaluation is used to determine test performance when the test is performed by clinic personnel who are not trained laboratory technicians. It is also important to assess minimal operational characteristics of the POCT such as the ease of use, acceptability of the tests to patients and healthcare providers when the tests are performed by clinic staff or health providers.

This Core Protocol can be used for the clinic-based evaluation of POCTs targeted at a single or multiple pathogens. The number of swabs would need to be adjusted accordingly.

2.2 Study hypothesis and objectives

The overall objective of the World Health Organization (WHO) Point-Of-Care (POC) Diagnostics Evaluation Scheme for Sexually Transmitted Infections (STI) is to provide advice to WHO Member States and other relevant public health institutions on the performance and operational characteristics of commercially available STI diagnostic tests that can be used at the point-of-care (hereafter referred to as POCTs). The specific objectives of this clinic-based evaluation of POCTs for the screening of asymptomatic genital, anorectal and pharyngeal chlamydial and gonococcal infections, as recommended by the WHO guideline for HIV and STI prevention and treatment, in men who have sex with men (MSM) are:

1. To determine the performance of POCTs for the screening of genital, anorectal and pharyngeal chlamydial and gonococcal infections in MSM compared to that of nucleic acid amplified tests (NAATs) as a reference standard

2. To assess the operational characteristics and acceptability of these POCTs to patients and healthcare providers

2.3 Study conceptual framework

Question: Are point-of-care tests for the screening of genital, anorectal and pharyngeal chlamydial and gonococcal infection in MSM as performant as the gold standard tests?

P (participants): MSM > 18
I (intervention): perform the Ct, Ng POCT in accordance with the manufacturers’ directions
C (control): perform the Ct, Ng, gold standard diagnostic tests on the same person at the same time
O (outcome): sensitivity, specificity, predictive values and operational characteristics
T (timeframe): until the required sample size is reached, with a maximum of 12 months

2.4 Study design

The evaluation should be conducted according to the following guiding principles:

1. A diagnostic test should be evaluated for a clearly defined indication
2. A diagnostic test should be evaluated using methods and equipment fit for that purpose
3. Staff performing the evaluation should be qualified and competent to undertake the task and demonstrate that they can perform the test properly through proficiency testing programme results
4. There should be a regular independent assessment of the laboratory quality assurance and quality control procedures, and of the proficiency of the laboratory to do the reference tests for evaluation, and whether the evaluations are conducted in compliance with the Principles of Good Clinical Practice (GCP) and Good Clinical Laboratory Practice (GCLP).

2.5 Procedures

2.5.1 Study site(s)
Evaluation sites consist of central laboratories with a network of POC sites that fulfils the following criteria:

- Routine availability of laboratory Ng/Ct testing and counselling services for MSM
- Familiarity of working with the target population, MSM: a clinical site could be an MSM-friendly clinic (department) or another low threshold STI and/or sexual health service for MSM, such as an outreach programme, operated by the government or NGOs, depending on the site
- Evidence of ongoing accreditation for laboratory quality management systems
- Access to sufficiently large target population to be able to complete patient recruitment for the evaluation in 9-12 months
- Ability to meet expected turn-around time for patient results with reference technology platform and expected turn-around time for POCTs
- Mechanism for ethical committee approval in 2-3 months
- Demonstration of proficiency in performing reference standard technologies in an international proficiency programme (defined as ≥ 90% score on minimum of 2 proficiency testing events in the last 12 months)
- Human resources: sufficient trained laboratory and POC site staff capacity to be able to perform the study in accordance with the study protocol
- Strong interest to work with new technologies

2.5.2 Study participants

Inclusion criteria:
The target populations for this Ct and Ng POCT evaluation are MSM. According to the UNAIDS Action Framework, the term ‘men who have sex with men’ is defined as those males who have sex with other males, regardless of whether or not they have sex with women or have a personal or social identity associated with that behaviour, such as being ‘gay’ or ‘bisexual’.

Antibiotic usage in MSM who have been prescribed antibiotics for any of the above infections or any other infections 3 weeks prior to study entry should be recorded in the data collection form but not used as a criterion for exclusion.

Exclusion criteria:
MSM who are less than 18 years of age or who refuse to give consent.

There is no mention of transgender persons in this protocol for the clinic-based validation of POCTs for the screening of genital and extragenital chlamydial and gonococcal infections, because there is no consolidated clinical definition of what constitutes a transgender person.

2.5.3 Participant recruitment

Consecutive MSM presenting to the clinic at the evaluation sites or outreach settings will be informed about the study by a health care provider. If the MSM is interested in participating (pre-consent), another health care provider will evaluate whether he fits the inclusion criteria. If the potential participant fits the criteria and agrees to participate in the study, the latter health care provider will take final consent and perform the routine care and the additional tests. Patients will be informed by the healthcare provider and the consent form (consent form, Appendix 1).

2.5.4 Sampling and allocation

Prospective sampling.

2.5.5 Sampling size calculation

The sample size calculation depends on the estimated performance of the POCT compared to the reference standard and the prevalence of infection at the study site. For example, if it is estimated that the sensitivity of a new test is 80% compared to the reference standard, then 200 infected study subjects by the reference
standard test would need to be recruited for a confidence interval of ± 5% around the point estimates of sensitivity and specificity (table sample size/CI, Appendix 2). If the prevalence of infection in the study population is 10%, then there will be 10 infected subjects per 100 patients seen at the clinic. Then 2,000 (100/10 x 200) patients will need to be recruited.

To conduct the studies in a timely manner, it is likely that a network of sites will be needed to contribute 200 positive samples for the evaluation of each pathogen in the POCT.


2.5.6 Description of the intervention

2.5.6.1 Drugs and devices

POCTs for STIs are described in a landscape report commissioned by WHO RHR. Tests that have operational characteristics that are consistent with the Target Product Profiles and have acceptable analytical performance characteristics are invited to participate in the clinic-based evaluations. A letter announcing the evaluation will be sent the relevant companies with details of the evaluation including the core protocols. Companies interested in participating in the evaluation are asked to donate tests for the clinic-based evaluations in accordance with the terms specified under a WHO confidentiality and material transfer agreement.

2.5.6.2 Innovation in service delivery

To increase access to screening and diagnostic testing, it is important that the tests to be included in this evaluation should have characteristics that are consistent with those set out in the Target Product Profiles (TPPs) developed by consensus at the first WHO RHR Technical Consultation on POCTs for STIs in 2014. These include the following operational characteristics:

1. Rapid -- test result is available within the duration of the clinic visit.
2. Simple -- test can be performed in 2-3 steps, requiring minimal training and no equipment
3. Easy to interpret -- card or strip format with visual readout or using a small reader

2.5.7 Admission procedure

Patients who give consent will undergo an interview and a physical examination according to routine clinic protocol at the site. In addition, they will be asked questions as specified in the WHO POC Diagnostics Evaluation Data Collection Form (Appendix 3). Three types of specimens will be collected: Urine, 2 oropharyngeal swabs taken simultaneously and 2 anorectal swabs taken simultaneously. A meatal swab can also be considered but it will increase the cost of the evaluation and its added value to the above specimens is unclear.

In addition to quantitative evaluation of test performance and reproducibility, qualitative assessment of the suitability and acceptability of the POCTs will be assessed by the staff member who performs the POCTs after he or she has completed the first 50 POCTs:

Suitability of test for use in primary healthcare settings:
- clarity of kit instructions (only for those who are familiar with the language in which the instructions are written)
- ease of use (technical complexity)
- ease of interpretation of results
- time to complete the test
- training time
- hands-on time

Other characteristics that can be scored but are not subjective are:
- duration of storage at room temperature
- additional material required
- number of steps required

Acceptability of POCTs to patients will be determined by asking the patients, if a good POCT is available, would they be willing to wait 30 min., 1 hour or 2 hours versus returning several days later for the test results (score of 0 to 3, 0 being unwilling to wait and 3 being willing to wait for 2 hours).

2.5.8 Follow-up procedures

Patients with a positive reference test result will be treated according to the standards of care as described in the national guidelines. POCT results will not be used for the treatment of patients.

2.5.9 Criteria for discontinuation of a participant

If during the procedure it would turn out that the patient does not meet the inclusion criteria. If the patient wishes to discontinue participation.

2.5.10 Criteria for discontinuation of the study

The study should only proceed when the study team members are confident of their ability to conduct the study and all the materials required for the study are in place. The study will be discontinued if during the study it would become apparent that despite the principal approval, the evaluation site, consisting of a central laboratory with a (network of) POC site(s), does not fulfil the inclusion criteria. If the study monitor sent by WHO deems as impossible that the site can guarantee the required progress and quality of the study. If external events prevent the study from being executed with the required quality.

2.5.11 Laboratory and other investigations

Three types of specimens will be collected: Urine, 2 oropharyngeal swabs taken simultaneously and 2 anorectal swabs taken simultaneously. Each sample/swab should be labelled with a study number, date and a code that indicates the specimen type. Dacron or cotton swabs should be used for specimen collection if the type of swab is not specified in the test kit instructions. Use of antiseptics, analgesics and lubricants when collecting specimens should be avoided as these substances may be inhibitory for laboratory tests.

The swabs should be collected by the health provider and placed into labelled dry collection tubes. The POCTs will be performed on one of each of the oropharyngeal or anorectal swabs.

Urine samples can be used for the POCT if the manufacturer has a claim on urine specimens. Urine samples will also be used for the reference test. They should be transported to the laboratory in accordance with standard operating procedures at the clinic.

If the POCT has a visual readout, each test result should be read independently by two clinic staff members to determine variability in the interpretation of test results. Results of POC and reference tests for each specimen will be recorded in an Excel spreadsheet provided by WHO.

The reference or "gold standard" test for this evaluation is a NAAT which should be performed on a urine sample and each of the oropharyngeal or anorectal swabs. All reference tests should be performed in accordance with the manufacturer’s directions and laboratory staff should be blinded to the POCT results.

Patients with a positive reference test result will be treated according to the standards of care as described in the national guidelines. POCT results will not be used for the treatment of patients.
2.6 Study instruments

Appendix 3. Clinic data collection form

Appendix 4. Laboratory data collection form

Appendix 5. Operational characteristics of POCTs

2.7 Project management

WHO will enter into an agreement with all the sites setting out the terms of reference for these evaluations. The site will have a study management plan with the details of the roles and responsibilities of the study team well-defined. WHO will send study monitors to perform external quality assessments of each evaluation. The study team at each evaluation site shall consist of a principal investigator who co-ordinates the entire study at the site, a clinical/technical supervisor, and field and laboratory staff members. The composition and number of study team members can be adapted at each site according to local needs. Their responsibilities are:

Principal investigator:
- participate in the development of the consensus protocol
- obtain ethical committee approval for the evaluation
- ensure the evaluation is conducted according to the consensus protocol as approved
- send data to WHO for collation with data from other sites
- participate in the overall review and analyses of evaluation results
- prepare a site technical and financial report of the evaluation

Clinical/Technical supervisor:
- supervise the pilot run and the day to day clinic activities that are related to the POCT evaluation, such as patient recruitment, interview, specimen collection, labelling, storage and transport to the laboratory
- ensure that laboratory technicians are blinded to the POCT results
- ensure that the results of the POCTs are read independently by 2 staff members
- sign off the log book of test results for staff member 2 and 3 and the laboratory staff at the end of each day
- collate the results from the clinic and laboratory staff and enter them into the Excel spreadsheet provided by WHO

Staff member 1:
- inform incoming patients about the study in a general way, without going into the specifics of the target population to avoid self-disclosure of the MSM-status of the patient
- gauge for interest in participating in the study
- record pre-consent
- inform staff member 2 if the patient has pre-consented

Staff member 2:
- check whether the patients who pre-consented fit the inclusion criteria
- take final consent if the patient fits the criteria and agrees to participate
- perform patient interviews
- collect samples
- perform POCTs in accordance with manufacturers’ directions
- record results in a log book
- ensure that the log book is stored safely (locked place, accessible only by members of the research team)
- place completed tests in folder for staff 3 to read

Staff member 3:
- read independently the results of POCTs conducted by staff 2 within the time defined by the manufacturers and after 1 hour to assess end-point stability
- record results in separate log book from that used by staff 2

Laboratory staff:
- perform reference standard tests
- record results in a laboratory record book

The study team should have training in the principles and practice of GCP and GCLP with specific reference to the evaluation protocol. Study monitors will be sent by WHO to each site at 3-monthly intervals to monitor the progress and quality of the study. The reference standards for Ct and Ng POCTs are NAATs as described in the WHO Manual for the Laboratory Diagnosis of Sexually Transmitted Infections. As part of site preparation, each site will be asked to perform NAAT testing on a proficiency panel sent by a WHO reference laboratory to all the sites. Evaluation of POCTs at each site can only proceed after satisfactory proficiency results for the reference test. This will also serve to standardize testing results from different sites.

The clinic staff should be trained in proper methods of specimen collection and handling. Staff members 2 and 3 should also be trained in the performance of the POCTs and the reading of testing results. At each site, the field staff member(s) who performs the POCTs should try out the testing procedure with positive and negative control specimens (can be requested from WHO if necessary) under the supervision of the technical supervisor. The POCTs should be read independently by both field staff members. If the results are invalid, the testing should be repeated with a new test. The test will be recorded as “Invalid” if the result of the repeated test is still invalid. The study should only proceed when the study team members are confident of their ability to conduct the study and all the materials required for the study are in place. Sites encountering problems with the evaluation should contact Dr. Igor Toskin for technical support.

2.8 Data quality assurance

The site supervisor should ensure that all staff involved in testing are proficient at performing the tests. Quality control samples should be introduced randomly for quality assurance. Quality of the overall study will be monitored by external monitors sent by WHO.

2.9 Data management

Depending on the site. Will be specified in the site consensus protocols. Data from the study will be kept for a minimum of one year after publication of its results and will then be destroyed.

Evaluation of diagnostic tests only requires specimens from the subject. The subject is not affected in any way; he/she does not ingest anything or is he/she injected with any experimental material and the result of the evaluation is not used to treat the patient. Therefore it is exempted from having a DSMB.

2.10 Data analysis plan

Data from the evaluation will be entered into a standardised spreadsheet for analyses. Double entry reduces chances of error. A positive case is defined as a patient with a positive reference standard test result regardless of specimen type. The sensitivity, specificity, positive and negative predictive values for each POCT will be calculated by comparing the POCT results to the validated reference test results as follows:

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<tr>
<th>Reference test results</th>
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<td>+</td>
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<tr>
<td>a</td>
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<tr>
<td>c</td>
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<td>a+c</td>
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POCT results

+ -
POCT sensitivity = \( a/(a+c) \)  Positive predictive value = \( a/(a+b) \)
POCT specificity = \( d/(b+d) \)  Negative predictive value = \( d/(c+d) \)

Any discrepant analysis will be conducted under advice from the WHO/TDR-LSHTM Diagnostic Evaluation Expert Panel. Inter-observer variability is calculated as the number of tests for which different results are obtained by 2 independent readers, divided by the number of specimens tested. The end-point stability of the test an hour after the test was performed will be calculated as % of test results that remain the same as the initial reading. The suitability and acceptability of the POCT for use in primary healthcare settings in developing countries will be assessed qualitatively and quantitatively through a simple descriptive statistic as described.

2.11 Study timeline

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<tr>
<th>Timeline</th>
<th>Jan</th>
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<th>Mar</th>
<th>Apr</th>
<th>May</th>
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<td>Finalise study protocol by adapting the core protocol</td>
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<td>Submit to WHO ethics committee</td>
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<td>Submit to local ethics committee, when necessary</td>
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<td>Obtain ethical approvals</td>
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<td>Validate proficiency at performing the reference test</td>
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<td>Train staff on the study protocol</td>
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<td>Prepare supplies and reference testing kits</td>
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<td>Receive testing kits under evaluation</td>
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<td>Pilot SOPs</td>
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<td>Conduct evaluation</td>
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<td>Analyse the study data</td>
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<td>Send testing results to WHO</td>
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<td>Provide results for selection in clinic-based evaluation</td>
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<td>Prepare the evaluation report</td>
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<td>Disseminate the study results</td>
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2.12 Main problems anticipated and proposed solutions

Will be included in the consensus protocols as they are site-specific.

2.13 Applicability of results

POCTs with acceptable levels of performance can improve access to testing and the timely detection and treatment of Ng/Ct in all clinic-based settings.

2.14 Links with other projects

Laboratory-based evaluations of POCTs will be the source of the POCTs used for the clinic-based evaluations. Clinic-based evaluations of POCTs for Ct and Ng will not only be done in screening of MSM, but also for Ct, Ng and Tv in screening of women with high risk of these infections and in case management of women complaining of VDS. Eligible POCTs for dual diagnose of HIV-syphilis will also be evaluated in clinic-based settings.
2.15 References

3. Gender considerations

3.1 Describe how women and men are affected by the public health need that the study addresses, and whether this is a need expressed or felt by women and/or men

MSM are at high risk of acquiring and transmitting STIs, but they may not present to clinics when they are asymptomatic because they are marginalised from the healthcare system. Moreover, these STIs are often asymptomatic. Undetected infection can result in serious long-term complications and increased risk of HIV acquisition and transmission. Screening and appropriate treatment for infections in asymptomatic individuals can reduce the risk of developing serious long-term complications, interrupt onward transmission to sexual partners and possibly the exchange of genetic elements between commensal and pathogenic Neisseria species that confer antimicrobial resistance.

3.2 Explain how the research contributes to identifying and/or reducing inequities between women and men in sexual and reproductive health and healthcare

MSM might find it difficult to access sexual health services. POCTs will enable them to be tested and if needed, treated in one single visit.

3.3 Describe measures taken to facilitate the individual participation of women or men in the research process in light of their different life situations.

NA, prospective sampling in clinic settings.

3.4 Describe measures taken to ensure that community involvement is inclusive.

NA, prospective sampling in clinic settings.

3.5 Describe the sex composition of the research team, and their duties and responsibilities in the proposed research.

NA, will be added in site specific consensual protocols.

4. Ethical issues

4.1 Ethical considerations:

The core protocol should be approved by the WHO Ethics Review Committee. Each evaluation site must obtain institutional review board or ethical committee approval for performing the evaluations in accordance with the final site protocol. The letter of approval with the names and affiliation of all the members of the ethical committee should be signed by the chair of the committee on behalf of the committee members and sent to WHO for documentation. An agreement with WHO can only be provided to the sites on receipt of documentation of local ethical approval.

4.1.1 Study population, recruitment strategy and informed consent process

MSM presenting in care will be informed about the study and their (non-)participation will not affect the standards of care that they receive in the clinic. Pre-consent and routine care integrated research activities will be handled by two separate health care providers.
4.1.2 Perceived risks and benefits of the study, both at the individual and community levels

A small amount of discomfort might be felt during specimen collection. There will be no immediate benefits in the participation in the study. When the study results are known and if the rapid tests are found to be acceptable in terms of accuracy, patients may benefit from having a POCT available to diagnose Ct and Ng and receive the treatment.

4.1.3 Safeguards to protect any recognized vulnerability of the study participants

The records concerning the participation are to be used only for the purpose of the research project. Names will not be used on any study form or label on laboratory specimens or in any report resulting from the study. At the beginning of the study, a study identification number will be given and this number will be used on the forms and on the laboratory specimens. Any information obtained in connection with this study will be kept strictly confidential. Only members of the study team (doctors, nurses and social workers) will have access to information linking a name with a study number. Autonomy of the patients to decide to participate in the study will be safeguarded by the division of the roles of taking pre-consent on the one hand and performing the study, integrated in routine care, on the other. The final consent has to be taken by the investigator, as he/she will also check the if the patient fits the inclusion criteria, for confidentiality reasons.

4.1.4 Reimbursement or compensation to study participants

There will be no monetary compensation for this study, but routine medical consultation and appropriate referral services will be provided.

4.1.5 Access to treatment or counselling for conditions either identified during screening of potential participants or resulting from the study intervention

If agreement to participate in the study is given, the doctor or nurse will conduct a routine medical examination and ask some questions according to standard clinic procedure. Treatment/intervention will be received based on the standard laboratory-based test results rather than POCT test result.

4.1.6 Responsiveness of the project to community needs and priorities

The introduction and withdrawal of the intervention will have no influence on the community. The product evaluated might be bought by countries for use in clinic-based settings, benefitting the community.

4.1.7 Deception

NA

4.2 Forms required (include or attach as a scanned copy, as appropriate)

4.2.1 Information sheet for participants and/or responsible persons

Appendix 1

4.2.2 Informed consent forms for participants and if appropriate, responsible persons

Appendix 1

4.2.3 Local (institutional, community and/or national) ethics approval

NA
5. **Environmental impact of the project**  
Biosafety guidelines for clinic and laboratory staff  

- Treat all specimens as potentially infectious  
- Wear protective gloves and laboratory gown while handling specimens  
- Do not eat, drink or smoke in the laboratory  
- Do not wear open toe footwear in the laboratory  
- Clean up spills with appropriate disinfectants e.g. 1% bleach  
- Decontaminate all materials with an appropriate disinfectant  
- Dispose of all waste, including test kits, in a biohazard container

6. **Plans for dissemination and use of project results**  
Results from this evaluation will be published in a WHO report for member states and posted on the WHO STI website.

7. **Other support for the proposed research project**  

7.1 Project support by other institution(s)  
Site specific.

7.2 Consideration of the proposal by other institution(s)  
NA

8. **Other current research projects of the principal investigator.**  
NA  
Please list all other research projects currently in progress.

<table>
<thead>
<tr>
<th>Title of project</th>
<th>Source of support</th>
<th>Duration of project (dates)</th>
<th>Per cent of time spent on project by principal investigator</th>
</tr>
</thead>
</table>

9. **Curricula vitae of the principal investigator and co-investigator(s)**  
NA
10. **Additional Information**

**Appendix 1. Patient information and consent form**

**A. Purpose of the study**

Chlamydia and gonorrhoea are infections caused by bacteria, which are transmitted by sexual intercourse. Undetected infection can result in serious long-term complications and increased risk of HIV acquisition and transmission.

In order to diagnose these infections, we need to do some laboratory tests. These tests are expensive and the results are not available the same day. Point-of-care (POC) tests to diagnose these infections within the same clinic visit are now available but we do not know if they are accurate or reliable.

The main purpose of this study is to evaluate a POCT for the diagnosis of these infections. We would like to compare the result of these POCTs with a laboratory-based test to see if they are as accurate as laboratory tests.

**B. Procedures to be followed**

If you agree to participate in the study, you will be assigned a study number. The doctor or nurse will give you a physical examination and ask you some questions according to standard clinic procedure. A urine sample, N samples from your urethra, throat, anus will be collected. Your name will not appear on any samples or on the questionnaire. All the samples will be destroyed at the end of the study.

**C. Voluntary participation**

A decision not to participate or to withdraw from participation will not affect the care you will receive at the clinic in any way. Even if you do agree to become a study participant, you can withdraw from study at any time (verbally). During the interview, you can choose not to answer any particular question.

**D. Discomfort and risks**

You may feel a small amount of discomfort during specimen collection.

**E. Benefits**

There are no direct benefits for you in taking part in the study. When the study results are known and the POCTs are acceptable in terms of accuracy, everyone who comes to the clinic may benefit from having this test available to diagnose these infections and receive the right treatment the same day.

**F. Compensation**

There will be no monetary compensation for this study, but routine medical consultation and appropriate referral services are available.

**G. Confidentiality statement**

The records concerning your participation are to be used only for the purpose of this research project. Your name will not be used on any study forms or labels on laboratory specimens or in any report resulting from this study. At the beginning of the study, we will give you a study identification number and this number will be used on the forms and on the laboratory specimens. Any information obtained in connection with this study
will be kept strictly confidential. Only members of the study team (doctors, nurses) will have access to information linking your name with your study number. If, at any time of your medical exam, the doctor doesn’t diagnose urethral, anal or pharyngeal infection (and, hence, doesn’t give you specific antibiotics) but the laboratory test detects any of these infections, we will treat you when you come back to the clinic to get your results. If you do not come back to the clinic within the following 10 days, a field worker will notify you to come back to the clinic.

H. Questions and freedom to withdraw from the study

You may withdraw from the study at any time without affecting your present or future medical care at the clinic. You may contact any of the study physicians if you have questions about the research. You may speak with the staff at the clinic (name ____________ _). You can also call the clinic during working hours at tel.: ____________.

I. Results publication

Data from the study will be kept for a minimum of one year after publication of its results. When the researchers will have analysed the data, the results and the explanation of its implications will be posted at the clinic for everyone’s information.

J. Participant statement

I have been informed verbally and in writing about this study and understand what is involved. I also know whom to contact if I need more information. I understand that confidentiality will be preserved. I understand that I am free to withdraw from the study at any time without affecting the care I normally receive at the clinic. I agree to participate in this study as a volunteer subject and will be given a copy of this informed consent to keep.

_________________  ______________________________________________
Date  Name of volunteer

________________________________________________
Signature (or thumb print or cross) of volunteer

_________________  ______________________________________________
Date  Name of witness

________________________________________________
Signature of witness

K. Investigator’s statement

I, the undersigned, have defined and explained to the volunteer in a language he understands, the procedures of this study, its aims and the risks and benefits associated with his participation. I have informed the volunteer that confidentiality will be preserved, that he is free to withdraw from the study at any time without affecting the care he will receive at the clinic. Following my definitions and explanations the volunteer agrees to participate in this study.

_________________  ______________________________________________
Date  Name of investigator who gave the information about the study

Signature: ____________________________________________
Appendix 2. Relationship between sample size and 95% confidence interval

<table>
<thead>
<tr>
<th>Number of infected (non-infected) subjects required*</th>
<th>Estimated test sensitivity (or specificity)(^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>50%</td>
</tr>
<tr>
<td>50</td>
<td>13.9%</td>
</tr>
<tr>
<td>100</td>
<td>9.8%</td>
</tr>
<tr>
<td>150</td>
<td>8.0%</td>
</tr>
<tr>
<td>200</td>
<td>6.9%</td>
</tr>
<tr>
<td>500</td>
<td>4.4%</td>
</tr>
<tr>
<td>1,000</td>
<td>3.1%</td>
</tr>
</tbody>
</table>

*As defined by the reference standard test. *95% confidence interval around the estimated sensitivity (+/- value in table).

Appendix 3. Clinic data collection form

**Study number**: abbreviation for site location + consecutive no. 001-1000

**Date of clinic visit:**

**Study site:**

*Date of birth*: ________________ (day/month/year)

**Assessment of STI risk:**

- Accepted money or goods for sex: Y/N
- Unprotected sexual oral and/or anal intercourse (insertive/receptive) with more than one partner in the last 12 months: Y/N
- Reported past history of STIs: Y/N

**Symptoms**: yes________ (tick all that is applicable below); no______

- Urethral discharge: Y/N
- Anal discharge: Y/N
- Dysuria: Y/N
- Others: specify___________________________________________

**Physical examination:**

- Urethral discharge: Y/N
- Anal discharge: Y/N
  - if Y, colour___, profuse___/scanty___

If a POCT is available at this clinic, are you willing to wait for test results: Y/N
If Y, will you wait 30 min. ____ , 1 hour ____ , 2 hours ____?
## Appendix 4. Laboratory data collection form

Name of test:  
Manufacturer:  
Lot number:  
Expiry date:  
Evaluation site:

<table>
<thead>
<tr>
<th>Study #</th>
<th>Date and type of specimen</th>
<th>POCT Results</th>
<th>Reference Test Result</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Reader 1</td>
<td>Reader 2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>15 min</td>
<td>60 min</td>
<td></td>
</tr>
</tbody>
</table>
Appendix 5. Operational characteristics of POCTs

Name of kit:

Manufacturer:

Name of staff member:

<table>
<thead>
<tr>
<th>Score</th>
<th>Clarity of kit instructions</th>
<th>Score</th>
<th>Ease of use</th>
<th>Score</th>
<th>Ease of interpretation of results</th>
<th>Score</th>
<th>Rapidity of test results</th>
<th>Score</th>
<th>Hands-on time</th>
<th>Score</th>
<th>Training time required</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>difficult to follow</td>
<td>0</td>
<td>complicated</td>
<td>0</td>
<td>difficult</td>
<td>0</td>
<td>&gt;30 minutes</td>
<td>0</td>
<td>10 minutes</td>
<td>0</td>
<td>&gt;1 hour</td>
</tr>
<tr>
<td></td>
<td>fairly clear</td>
<td>1</td>
<td>fairly easy</td>
<td>1</td>
<td>fairly easy</td>
<td>1</td>
<td>20-30 minutes</td>
<td>1</td>
<td>5 minutes</td>
<td>1</td>
<td>1 hour</td>
</tr>
<tr>
<td></td>
<td>very clear</td>
<td>2</td>
<td>very easy</td>
<td>2</td>
<td>very easy</td>
<td>2</td>
<td>&gt;20 minutes</td>
<td>2</td>
<td>&lt;5 minutes</td>
<td>2</td>
<td>30 minutes</td>
</tr>
<tr>
<td></td>
<td>excellent</td>
<td>3</td>
<td>unambiguous</td>
<td>3</td>
<td>unambiguous</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;30 minutes</td>
</tr>
</tbody>
</table>

5. Hands-on time

<table>
<thead>
<tr>
<th>Score</th>
<th>&lt;5 minutes</th>
<th>2</th>
</tr>
</thead>
</table>

6. Training time required

<table>
<thead>
<tr>
<th>Score</th>
<th>&lt;30 minutes</th>
<th>3</th>
</tr>
</thead>
</table>
Appendix 6. Budget template

Budget template for Evaluation of POC STI diagnostics: Costing based on patient recruitment for 9 months and study completion by 12 months.

<table>
<thead>
<tr>
<th>Item</th>
<th>Cost (USD)</th>
<th>Subtotal/Total (USD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Personnel:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Study coordinator (0.5 FTE)</td>
<td>35,000</td>
<td>35,000</td>
</tr>
<tr>
<td>2. Technician</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Clinic health worker</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Data manager (0.5 FTE)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Supplies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(consumables: gloves, pipettes, etc)</td>
<td>3,000</td>
<td></td>
</tr>
<tr>
<td><strong>Reference testing</strong></td>
<td>10,000</td>
<td>13,000</td>
</tr>
<tr>
<td><strong>Travel</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local travel (field work)</td>
<td>2,000</td>
<td>2,000</td>
</tr>
<tr>
<td><strong>GCP/GCLP Training and mentoring</strong></td>
<td>1,500</td>
<td></td>
</tr>
<tr>
<td><strong>Communication</strong></td>
<td>500</td>
<td></td>
</tr>
<tr>
<td><strong>Publishing</strong></td>
<td>2,000</td>
<td>4,000</td>
</tr>
<tr>
<td><strong>Other (please specify and justify below)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TOTAL BUDGET</strong></td>
<td></td>
<td>54,000</td>
</tr>
</tbody>
</table>

The study budget does not include: 1) the full cost of reference testing as the evaluation will be conducted in sites where reference technologies are part of the standard of care; 2) costs of POCTs as these will be provided from the companies. International travel for research staff will be budgeted separately.