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Thematic area:

Single site proposal

"Core" proposal (for multicentre study)

Centre-specific proposal under multicentre study

Connect ID No:

Form II

HRP Research Proposal: Project details

Clinic-based Evaluation of Dual Point-Of-Care Tests for the Screening of HIV and Syphilis in Pregnant Women

1. Project summary

a. Background information and rationale

Serologic tests are the diagnostic tests of choice for HIV and syphilis. There are two types of serological tests (treponemal and non-treponemal tests) for laboratory diagnosis of syphilis. Traditionally, one non-treponemal assay is used for screening and a treponemal assay is used for confirmation for syphilis. For diagnosis of HIV EIAs are used for screening and Western blot for confirmation for HIV in high-resource settings. However, these tests are technically demanding, and require laboratory equipment that is not widely available in most resource-limited settings. Recently, dual tests that can be used at point-of-care for simultaneously detecting antibodies to HIV and syphilis (dual HIV-syphilis POCTs) have been developed for use with venous whole blood, serum/plasma, or finger-pricked capillary whole blood. Some of these dual POCTs are now commercially available. To date, they have shown encouraging performance compared with the reference tests in laboratory-based studies, but there is limited data on their performance in the field. Therefore, evaluation of the performance of these dual tests in clinic-based settings and their acceptability to patients and healthcare providers are therefore a high priority.

b. Study hypothesis and objectives

The overall objective of the World Health Organization Point-Of-Care 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. A number of tests that can simultaneously detect antibodies against HIV and *Treponema pallidum* (Tp) from a single finger-pricked capillary whole blood specimen have been developed. The specific objectives of this clinic-based evaluation of POCTs for the screening of HIV and syphilis in pregnant women are to determine the performance of dual POCTs for the screening of HIV and syphilis compared to that of laboratory based HIV ½ Enzyme Immunoassay (EIA) and the *Treponema pallidum* Passive Particle Agglutination (TPPA) assay as reference standards and to assess the minimal operational characteristics and acceptability of these dual HIV-syphilis POCTs to patients and healthcare providers. As a secondary objective, the potential utility of these dual HIV-syphilis POCTs in identifying active syphilis will be determined using a combination of non-treponemal and treponemal tests as a comparator.

c. Study methods

Prospective sampled consecutive pregnant women presenting to the clinic at the evaluation sites and who fit the inclusion criteria will be asked to participate in the study. Patients will be informed by the health care 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 site. Since sites may have a different prevalence for HIV and syphilis, the evaluations may need to be conducted in a network of sites that have high and low prevalence for HIV and syphilis and the results analysed in aggregate to assure an adequate sample size as follows: Anti-HIV+ = 200, Anti-TP+ =200, Anti-HIV- =200, Anti-Tp - = 200. For the utility determination, quantitative non-Tp testing will be performed on all those who are Tp+ to determine the number of study participants who have active syphilis.

Three to five mL of venous blood will be collected and will be processed for reference testing within 12 hours of collection. The capillary whole blood sample will be collected and used immediately to perform the POCT according to manufacturer's instructions by a clinic or outreach healthcare provider. 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 dual 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

Serologic tests are the diagnostic tests of choice for HIV and syphilis. There are two types of serological tests (treponemal and non-treponemal tests) for laboratory diagnosis of syphilis. Traditionally, one non-treponemal assay is used for screening and a treponemal assay is used for confirmation for syphilis. For diagnosis of HIV EIAs are used for screening and Western blot for confirmation for HIV in high-resource settings. However, these tests are technically demanding, and require laboratory equipment that is not widely available in most resource-limited settings. Recently, dual tests that can be used at point-of-care for simultaneously detecting antibodies to HIV and syphilis (dual HIV-syphilis POCTs) have been developed for use with venous whole blood, serum/plasma, or finger-pricked capillary whole blood. Some of these dual POCTs are now commercially available. To date, they have shown encouraging performance compared with the reference tests in laboratory-based studies, but there is limited data on their performance in the field. Therefore, evaluation of the performance of these dual tests in clinic-based settings and their acceptability to patients and healthcare providers are a high priority.

The evaluation of these POCTs is important for two reasons. HIV and syphilis are often asymptomatic. Undetected syphilis can result in adverse outcomes of pregnancy and increased risk of HIV acquisition and transmission. Screening and appropriate treatment for these infections in asymptomatic individuals can reduce the risk of developing serious long-term complications and interrupt onward transmission to their sexual partners and the fetus in pregnant women. Dual POCTs with acceptable levels of performance can improve access to testing and the timely detection and treatment of HIV and syphilis in antenatal clinic settings. POCTs are thus an important tool for the prevention of mother-to-child transmission of HIV and the elimination of congenital syphilis.

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 dual POCTs such as the ease of use, acceptability of the tests to patients and clinic personnel at POC testing sites.

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). A number of tests that can simultaneously detect antibodies against HIV and *Treponema pallidum* (Tp) from a single finger-pricked capillary whole blood specimen have been developed. The specific objectives of this clinic-based evaluation of POCTs for the screening of HIV and syphilis in pregnant women are:

1. To determine the performance of dual POCTs for the screening of HIV and syphilis in pregnant women compared to that of laboratory based HIV ½ Enzyme Immunoassay (EIA) and the *Treponema pallidum* Passive Particle Agglutination (TPPA) assay as reference standards
2. To assess the minimal operational characteristics and acceptability of these dual HIV-syphilis POCTs to patients and healthcare providers

As a secondary objective, the potential utility of these dual HIV-syphilis POCTs in identifying active syphilis will be determined using a combination of non-treponemal and treponemal tests as a comparator.

2.3 Study conceptual framework

Question: Are dual point-of-care tests for the screening of HIV and syphilis in pregnant women as performant as the gold standard tests?

P (participants): Women > 18 pregnant, attending antenatal care

I (intervention): perform the dual HIV-syphilis POCT in accordance with the manufacturers' directions

C (control): perform the HIV and syphilis 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 HIV/syphilis testing and counselling services
- 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 $\geq 90\%$ 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 HIV-syphilis POCT evaluation are pregnant women presenting for antenatal care.

Antibiotic usage in pregnant women who have been prescribed antibiotic treatment for syphilis or other infections 3 weeks prior to study entry should be recorded in the data collection form but not used as criteria for exclusion.

Exclusion criteria:

Pregnant women who are younger than 18 years old or who refuse to give consent.

2.5.3 Participant recruitment

Consecutive pregnant women presenting to the clinic at the evaluation sites will be informed about the study by a health care provider. If the pregnant woman is interested in participating (pre-consent), another health care provider will evaluate whether she 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 health care providers 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 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 $\pm 5\%$ 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 ($100/10 \times 200$) patients will need to be recruited.

Since sites may have a different prevalence for HIV and syphilis, the evaluations may need to be conducted in a network of sites that have high and low prevalence for HIV and syphilis and the results analysed in aggregate to assure an adequate sample size as follows:

Anti-HIV+ = 200

Anti-Tp+ = 200

Anti-HIV- = 200

Anti-Tp- = 200

For the utility determination, quantitative non-Tp testing will be performed on all those who are Tp+ to determine the number of study participants who have active syphilis.

Detailed calculations can be found in Ref. WHO/[TDR Diagnostics Evaluation Expert Panel](#). Evaluation of diagnostic tests for infectious diseases: general principles. Nat Rev Microbiol 4(Suppl):S21-31, 2006.

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 TPPs 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). Two types of specimens will be collected:

1. Venous blood for laboratory based reference tests
2. Finger-pricked capillary whole blood for the dual POCT

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). Patients will also be asked if they prefer a single HIV syphilis test or duplex tests.

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. When 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 to five mL of venous blood should be collected and placed into labelled collection tubes with anticoagulant that does not interfere with the assays and transported to laboratory in accordance with standard operating procedures at the clinic. The venous blood sample should be processed for reference testing within 12 hours of collection. Serum can be stored at 2-8°C for up to 5 days before processing, and should be stored at -20°C if not processed by 5 days. The capillary whole blood sample should be collected and used immediately to perform the POCT according to manufacturer's instructions by a clinic or outreach healthcare provider. 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" tests for this evaluation are, for HIV: laboratory based HIV 1/2 EIA, confirmed by immunoblot; for syphilis: for the determination of Tp POCT performance, the reference is the TPPA. For the determination of potential utility, a probable active syphilis case is defined as non-Tp (such as rapid plasma reagin (RPR) test positive at a titre >8), confirmed by TPPA.

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
- 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
- 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 these dual POCTs are the laboratory based HIV 1/2 EIA and TPPA assay 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 reference 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. The site supervisor should send serum aliquots from all study participants with positive test results, 10% of negative results and any discrepant results to a WHO designated reference laboratory for validation. The quality of the evaluation 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. 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:

		Reference test results		
		+	-	
POCT results	+	a	b	a+b
	-	c	d	c+d

a+c	b+d	
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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

	Timeline							
	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug
Finalise study protocol by adapting the core protocol								
Submit to WHO ethics committee								
Submit to local ethics committee, when necessary								
Obtain ethical approvals								
Validate proficiency at performing the reference test								
Train staff on the study protocol								
Prepare supplies and reference testing kits								
Receive testing kits under evaluation								
Pilot SOPs								
Conduct evaluation								
Analyse the study data								
Send testing results to WHO								
Provide results for selection in clinic-based evaluation								
Prepare the evaluation report								
Disseminate the study results								

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

Dual POCTs with acceptable levels of performance can improve access to testing and the timely detection and treatment of HIV and syphilis in all antenatal clinic 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 HIV-syphilis will not only be done in screening of pregnant women, but

also in key populations such as men who have sex with men and sex workers. Eligible POCTs for diagnose of chlamydial, trichomonas and gonococcal infections 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

HIV and syphilis are often asymptomatic. Undetected syphilis can result in adverse outcomes of pregnancy and increased risk of HIV acquisition and transmission. Screening and appropriate treatment for these infections in asymptomatic individuals can reduce the risk of developing serious long-term complications and interrupt onward transmission to their sexual partners and the fetus in pregnant women. Dual POCTs with acceptable levels of performance can improve access to testing and the timely detection and treatment of HIV and syphilis in antenatal clinic settings. POCTs are thus an important tool for the prevention of mother-to-child transmission of HIV and the elimination of congenital syphilis.

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

While in some settings women might find it difficult to access sexual health services, screening in ANC is an opportunity for confidential testing of HIV and STI.

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 antenatal care

3.4 Describe measures taken to ensure that community involvement is inclusive

NA, prospective sampling in antenatal care

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 consensus 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

Pregnant women presenting for antenatal 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

There might be a small amount of discomfort while the blood is taken and some bruising might appear at the place where the blood is taken. The bruise should disappear in a short time. 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 combination rapid test available to diagnose HIV and/or syphilis 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.

Title of project	Source of support	Duration of project (dates)	Per cent of time spent on project by principal investigator
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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

HIV or syphilis infection can lead to serious adverse outcomes through transmitting the infection to your sexual partners and your baby. Early detection and treatment of these infections are important.

We can detect the infection with simple blood tests here at the clinic but they are separate tests and sometimes it may take a few days to get the results back to you. There are new combination tests available which can give us results for both HIV and syphilis from the same test within half an hour but we do not know if it is as accurate as the one we now use. We would like to ask for your help in comparing the new test to the test we normally use at the clinic. If the new test works well, perhaps in the future we will be able to give a more rapid diagnosis of both HIV and syphilis using a single test.

B. Procedures to be followed

If you agree to participate in the study, the doctor or nurse will give you a routine medical examination and ask you some questions according to standard clinic procedure. He/she will take 5 ml of blood from your vein as is the normal procedure at the clinic, and in addition we will collect two drops of blood from your fingertip to see if it works with the rapid test also. We will use a portion of your blood to do a rapid test in addition to the normal laboratory test. You will receive treatment or intervention based on the standard laboratory-based test results rather than the new combination rapid test result as we are not sure how accurate the new combination rapid test is.

C. Voluntary participation

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

D. Discomfort and risks

You may feel a small amount of discomfort while your blood is taken and you may have some bruising at the place where the blood is taken. The bruise should disappear in a short time.

E. Benefits

There are no direct benefits for you in taking part 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 combination rapid test available to diagnose HIV and/or syphilis and receive the treatment.

F. Compensation

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

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 form or label 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 and social workers) will have access to information linking your name with your study number.

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 staff 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.

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 she understands, the procedures of this study, its aims and the risks and benefits associated with her participation. I have informed the volunteer that confidentiality will be preserved, that she is free to withdraw from the study at any time without affecting the care she 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

Number of infected (non-infected) subjects required*	Estimated test sensitivity (or specificity) [†]					
	50%	60%	70%	80%	90%	95%
50	13.9%	13.6%	12.7%	11.1%	8.3%	–
100	9.8%	9.6%	9.0%	7.8%	5.9%	4.3%
150	8.0%	7.8%	7.3%	6.4%	4.8%	3.5%
200	6.9%	6.8%	6.4%	5.5%	4.2%	3.0%
500	4.4%	4.3%	4.0%	3.5%	2.6%	1.9%
1,000	3.1%	3.0%	2.8%	2.5%	1.9%	1.4%

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

Ref. WHO/[TDR Diagnostics Evaluation Expert Panel](#). Evaluation of diagnostic tests for infectious diseases: general principles. Nat Rev Microbiol 4(Suppl):S21-31, 2006.

Appendix 3. Clinic data collection form

1. Name of clinic: _____
2. Study number (combination of site abbreviation and a consecutive 4-digit number):
3. Date (day/month/year): _____/_____/_____
4. Age or Date of birth (day/month/year): _____/_____/_____ (_____ years)
5. Duration of gestation: _____ weeks
6. How long did it take for you get to the clinic from home? _____ hours
7. Have you had HIV testing before? [1] Yes [2] No [3] Don't know
 - 7.1. If yes, did you learn the test results? [1] Yes [2] No
 - 7.2. If yes, what result was it? [1] Positive [2] Negative
8. Have you have syphilis testing before? [1] Yes [2] No [3] Don't know
 - 8.1. If yes, did you learn the test results? [1] Yes [2] No
 - 8.2. If yes, what result was it? [1] Positive [2] Negative
 - 8.3. If positive, have you been treated? [1] Yes [2] No [3] Don't know
9. If we have a rapid test kit to simultaneously detect HIV and syphilis (dual test) and two single tests to separately detect HIV and syphilis, which one do you prefer?
[1] Dual (Jump to Question 10) [2] Single [3] Don't know/don't care
 - 9.1. If you prefer single test, why?
[1] Don't want be tested for HIV
[2] Don't want to be tested for syphilis
[3] Other (please describe): _____
10. If a rapid test is available at this clinic, would you be willing to wait for the results:
[1] Yes [2] No
 - 10.1. If yes, how long would you be willing to wait?
[1] 30 min. [2] 1 hour [3] 2 hours

Appendix 4. Laboratory data collection form

Data Recording Form (Study Clinic Site)

Name of test: _____

Manufacturer: _____

Lot number: _____

Expiry date (day/month/year): ____ / ____ / ____

Evaluation site: _____

Results read by: Staff member 1 Staff member 2

Study number	Date of specimen (day/month/year)	Initial results		POCT results after 1 hour (not for reader 1)	
		HIV	Tp	HIV	Tp
	/ /				
	/ /				
	/ /				
	/ /				
	/ /				
	/ /				
	/ /				
	/ /				
	/ /				
	/ /				
	/ /				

P = positive; N = negative; I = invalid (The test with invalid result should be repeated with a new test and the result will be recorded as “invalid” if the result of a repeated test is still invalid).

Appendix 5. Operational characteristics of POCTs

Name of kit:

Manufacturer:

Name of staff member:

	Score
1. Clarity of kit instructions	
difficult to follow	0
fairly clear	1
very clear	2
excellent	3
2. Ease of use	
complicated	0
fairly easy	1
very easy	2
excellent	3
3. Ease of interpretation of results	
difficult	0
fairly easy	1
very easy	2
unambiguous	3
4. Rapidity of test results	
>30 minutes	0
20-30 minutes	1
>20 minutes	2
5. Hands-on time	
10 minutes	0
5 minutes	1
<5 minutes	2
6. Training time required	
>1 hour	0
1 hour	1
30 minutes	2
<30 minutes	3

Appendix 6. Budget template

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

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

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.