Syphilis self-testing to expand test uptake among men who have sex with men (SST): A Pilot RCT in Zimbabwe and China

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STUDY COORDINATION CENTRE: LSHTM

LSHTM ethics reference: Pending

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Sponsor

London School of Hygiene & Tropical Medicine is the main research sponsor for this study. For further information regarding the sponsorship conditions, please contact the Research Governance and Integrity Office:

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Funder
This study is funded through an MRC/DFID/NIHR/Wellcome Joint Global Health Trials grant awarded to the investigators.

This protocol describes the Zim-China-SST study and provides information about procedures for entering participants. The protocol should not be used as a guide for the treatment of other participants; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study, but centres entering participants for the first time are advised to contact the trials centre to confirm they have the most recent version.

Problems relating to this trial should be referred, in the first instance, to the study coordination centre.

This trial will adhere to the principles outlined in the International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines, protocol and all applicable local regulations.

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GLOSSARY OF ABBREVIATIONS

HIV	Human Immunodeficiency Virus
LMIC	Low and Middle Income Countries
MSM	Men who have sex with Men
SST	Syphilis Self Testing
STI	Sexually Transmitted Infections
SAE	Serious Adverse Event
SUSAR	Serious Unexpected Event

KEYWORDS

Syphilis
Sexually Transmitted Infections
Self-Testing

STUDY SUMMARY

TITLE	Syphilis self-testing to expand test uptake among men who have sex with men (SST): A Pilot RCT in Zimbabwe and China
DESIGN	Single Blind Prospective Pilot RCT
AIMS	What is the effectiveness and cost-effectiveness of a community-based syphilis self-testing intervention (comprising a self-test kit integrated with HIV self-testing, simplified pictorial guidance, and photo-verification) to increase syphilis diagnosis and treatment among MSM (primary outcomes)? What is the effectiveness of the intervention to improve sexual behaviours, social outcomes, self-testing usability, and HIV test uptake (secondary outcomes)?
OUTCOME MEASURES	Proportion of individuals who undertake a syphilis test; among those who receive a test, the proportion of individuals who receive appropriate post-testing services. We will also collect qualitative data on attitudes to syphilis self-testing and quantitative data on syphilis prevalence to inform a subsequent clinical trial.
POPULATION	Two hundred MSM; 100 recruited in China and 100 recruited in Zimbabwe.
ELIGIBILITY	All residents of selected communities are eligible to participate in the study
INTERVENTION	*Syphilis Self Testing:* Treponemal rapid syphilis test kit to all individuals in the intervention arm of the pilot accompanied by simplified pictorial instructions on finger prick blood sample collection. *Control Group* Provision of a list of local clinics that can provide free syphilis testing.
DURATION	6 months

1. INTRODUCTION

1.1 BACKGROUND

Syphilis infection is a major global health problem, leading to substantial morbidity among key populations in low- and middle-income countries (LMICs). Men who have sex with men (MSM) are disproportionately affected by syphilis worldwide. Rates of syphilis diagnoses have been increasing amongst MSM in many countries in the last decade[1–4].

Though syphilis infection can be successfully treated with penicillin, most individuals with early stages of syphilis are asymptomatic and so they do not seek testing and treatment, resulting in onward transmission[5]. Therefore, expanding syphilis testing so that individuals receive a timely diagnosis and treatment, plays a key role in the control of syphilis transmission [6]. However, syphilis testing rates remain low among MSM in low- and middle-income countries (LMICs). Studies in several countries and the United Kingdom suggest that increases in syphilis screening are associated with increased detection of asymptomatic infectious syphilis with relative falls in secondary syphilis for both HIV-positive and HIV-negative MSM suggesting an interruption of syphilis progression [7–10].

1.2 RATIONALE FOR CURRENT STUDY

A growing evidence base supporting HIV self-testing shows that self-testing kits based on the same proposed clinical pathways are feasible and reliable[11,12]. The proposed study will leverage this body of evidence and apply it to syphilis self-testing. A small body of evidence suggests some MSM in China already use Syphilis Self Testing (SST)[13] but there is limited data about its use more broadly in LMICs and no prospective RCT data on whether SST may promote increased syphilis testing and linkage to care. There is momentum in China to expand syphilis testing among MSM and in Zimbabwe to make health services more MSM-friendly. This study will build on this momentum, moving forward syphilis prevention and control. Increasing syphilis testing and related service uptake among MSM may contribute to decreased HIV risk in this population.

2. STUDY OBJECTIVES

This is a pilot RCT designed to inform the design of a subsequent large scale RCT.

Study Aims:

What is the effectiveness and cost-effectiveness of a community-based syphilis self-testing intervention (comprising a self-test kit integrated with HIV self-testing, simplified pictorial guidance, and photo-verification) to increase syphilis diagnosis and treatment among MSM (primary outcomes)? What is the effectiveness of the intervention to improve sexual behaviours, social outcomes, self-testing usability, and HIV test uptake (secondary outcomes)?

Objectives:

i) Pilot a comprehensive HIV/syphilis self-testing intervention among 200 MSM over a period of six months

ii) Measure acceptability and feasibility of using syphilis self-test kits

iii) Optimise the use of sending a test kit photograph for results reporting

iv) Determine optimal methods for distributing self-test kits

v) Identify clinical sites in the two cities for facility-testing and linkage to care; vi) estimate the sample size for a future trial

vii) Estimate MSM retention within a self-testing trial

viii) Estimate the cost of intervention delivery and inform our future trial.

3. STUDY DESIGN

This is a pilot study conducted in China and Zimbabwe. It aims to collect initial data on the feasability of implementing syphilis self-testing to establish if a large scale-RCT of this approach would be appropriate and, if so, to inform the design of this trial.

Stage 1 Formative Work.

This element will be conducted only in Zimbabwe as we have previously conducted similar formative work in China.

Formative work will assess several questions

1) What is the best way to obtain confirmation of self-testing.

In China participants sent a photograph of their test result through an encrypted instant message to a coordinator; then men received a small incentive after uploading. We will explore practicalities and acceptability of this approach or alternative strategies in Zimbabwe.

2) We will field test our surveys on the experience of self-testing amongst MSM in Zimbabwe. We will base our initial survey instruments off tools used among Chinese MSM before and then refine them for use in the Zimbabwe component of the study.

Stage 2 Pilot RCT

We will recruit 100 MSM in Harare and 100 MSM in China to join the pilot program. Both settings have an active MSM communities that has been successfully engaged in previous HIV self-testing research.

Study Arms:

Arm 1: One arm of the pilot will receive a free syphilis self-test kit (Intervention Arm)

Arm 2: One arm will receive standard free facility-based syphilis testing (Control Arm).

Recruitment:

Men in both sites will be recruited through two methods: in-person at MSM community-based organizations that currently operate HIV self-testing programs and online through banner advertisements that advertise HIV self-testing. This was shown in our feasibility work to be an appropriate sampling frame for MSM.

Intervention:

In the intervention arm we will provide a treponemal rapid syphilis test kit to all individuals in the intervention arm of the pilot, delivered through MSM community facilitators or the mail. This is similar to

existing rapid treponemal test kits that are available at many clinical facilities. Participants may request a further SST kit at any point during the 6 months of follow-up. Kits will be accompanied by simplified pictorial instructions on finger prick blood sample collection. Among men in the control group, they will receive a list of local clinics that can provide free syphilis testing.

Data Collection:

For individuals in the intervention am we will aim to obtain photographic confirmation of test uptake. Men will send an encrypted instant message with a photograph of their test result to the local study coordinator. Among men who do not have a smart phone, they will send a unique five-digit code along with their test result to the study coordinator.

We will conduct cross-sectional surveys at baseline and six months later to assess sexual risk behaviours, HIV and syphilis testing experiences, and self-testing experiences. In addition to the survey data tool we will conduct in-depth interviews with a small number of participants to gain additional data about their experience of syphilis self-testing.

Duration

Participants in the Pilot RCT will be followed up to 6 months

3.1 STUDY OUTCOME MEASURES

Outcomes

PROPORTION OF INDIVIDUALS WHO UNDERTAKE A SYPHILIS TEST; AMONG THOSE WHO RECEIVE A TEST, THE PROPORTION OF INDIVIDUALS WHO RECEIVE APPROPRIATE POST-TESTING SERVICES. WE WILL ALSO COLLECT QUALITATIVE DATA ON ATTITUDES TO SYPHILIS SELF-TESTING AND QUANTITATIVE DATA ON SYPHILIS PREVALENCE TO INFORM A SUBSEQUENT CLINICAL TRIAL.

3.2 RISKS AND BENEFITS

If improved screening for syphilis translated to improved linkage to care then patients should receive earlier effective treatment for their syphilis. This would be anticipated to have direct benefits (prevention of morbidity related to syphilis) as well as potential for indirect benefits (reduced risk of HIV acquisition associated with syphilis). Patients who test positive for syphilis will be encourage to link to care where they will receive standard treatment for syphilis in line with national guidelines.

4. SELECTION AND WITHDRAWAL OF PARTICIPANTS

4.1 INCLUSION CRITERIA

Men who must meet the following criteria: currently residing in Guangzhou or Harare and planning to remain for the next six months; ever had anal or oral sex with another man; born biologically male; no history of syphilis testing in the past 12 months; at least one sexual risk factors (defined as condomless anal sex sex with a man, in a non-monogamous relationship with men, more than three male sexual partners, positive STI diagnosis in the past, currently taking HIV PrEP); 16 years or older; willing to provide a mobile phone number (for follow-up); have a stable residence where you can receive self-test kit packages (only for Guangzhou); able to provide informed consent.

4.2 EXCLUSION CRITERIA.

Individuals not consenting to participate in the study.

4.3 WITHDRAWAL CRITERIA

Study participation is voluntary and study participants can withdraw at any time. The number of withdrawals will be recorded and only data collected prior to withdrawal will be included in the analysis. Only data collected prior to withdrawal will be included in the analysis.

5. RANDOMISATION AND ENROLMENT PROCEDURE

5.1 RANDOMISATION OR REGISTRATION PRACTICALITIES

Individuals will be randomised by generating random numbers in STATA and generating a sequence for each of the two clinics. The assignment will be written on cards and placed in sealed envelopes.

5.2 BLINDING

This is a single-blinded study. It is not possible to blind participants as to whether they have undergone SST or not. Investigators responsible for performing the primary analysis (linkage to care) will be blinded to study arm.

6. TRIAL INTERVENTION

6.1 Name and description of investigational medicinal product(s)

We will use treponemal syphilis test kits that have already been approved by the Chinese Food and Drug Association. These kits are similar to HIV self-testing kits in terms of operation. They have excellent sensitivity, specificity. More details about these syphilis test kits is described in Wang et al., *Clinical Infectious Diseases*, 2019.

Syphilis Self-Test Arm

In the intervention arm we will provide a treponemal rapid syphilis test kit to all individuals in the intervention arm of the pilot, delivered through MSM community facilitators. This is similar to existing rapid treponemal test kits that are available at many clinical facilities. Kits will be accompanied by simplified pictorial instructions on finger prick blood sample collection.

Control Arm

Among men in the control group, they will receive a list of local clinics that can provide free syphilis testing.

7. SAFETY REPORTING

7.1 DEFINITIONS

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a patient or study participant
Serious Adverse Event (SAE)	A serious event is any untoward medical occurrence that: Results in death Is life-threatening Requires inpatient hospitalisation or prolongation of existing hospitalisation Results in persistent or significant disability/incapacity Consists of a congenital anomaly or birth defect Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.

7.2 REPORTING PROCEDURES

Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the Chief Investigator in the first instance.

7.2.1 Non serious AEs

The harms associated with self-testing are low. We will capture data on patient experience associated with self-testing through patient report and interviews using standard CRFs. Given the low risk nature of the intervention only unexpected non-serious AEs will be reported.

7.2.2 Serious AEs

Serious Adverse Events (SAEs) should be reported to the study coordination centre within 24 hours of the local site being made aware of the event. The harms associated with self-testing are low and there are no anticipated SAEs.

An SAE form should be completed and submitted to the study coordination centre with as much detail of the event that is available at that time. If awaiting further details, a follow up SAE report should be submitted promptly upon receipt of any outstanding information. SAEs will not require reporting or be considered to be SUSARs unless the severity of the event was considered to be unexpected.

Any events relating to a pre-existing condition or any planned hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

Contact details for reporting SAEs
Fax: xxx, attention xxx
Please send SAE forms to: xxx
Tel: xxx (Mon to Fri 09.00 – 17.00)

8. ASSESSMENT AND FOLLOW-UP

Baseline Data Collection

At baseline we will collect basic demographic data and data on sexual risk behaviours, HIV and syphilis testing experiences, and self-testing experiences.

Follow-Up Data Collection

For individuals in the intervention am we will aim to obtain photographic confirmation of test uptake. Men will send an encrypted instant message with a photograph of their test result to the local study coordinator. Among men who do not have a smart phone, there are two options for returning results: texting (using their analog mobile phone) a five-digit code along with test results to the study coordinator; dropping off the self-test kit at the local study site in Guangzhou or Harare, respectively.

We will repeat collection of data on sexual risk behaviours, HIV and syphilis testing experiences, and self-testing experiences at the end of the study period. In addition to the survey data tool we will conduct in-depth interviews with a small number of participants to gain additional data about their experience of syphilis self-testing.

Data on linkage to care will be obtained from administrative clinic records. Each site will provide the name of a single STD clinic where they can receive free treatment. In Guangzhou, this will be the Dermatology Hospital of Southern Medical University (2 Lujing Road, Guangzhou). In Harare, this will be a site chosen by the Pangaea Zimbabwe AIDS Trust based on previous research experience, penicillin availability, and key population training.

8.1 TRIAL CLOSURE

The trial is planned to run over a 6 month period. The trial will be complete at the end of this 6 month period.

9. STATISTICS AND DATA ANALYSIS

Sample Size

Given that this is a feasibility study, the primary purpose is to assess the feasibility of syphilis self-testing among MSM in China and Zimbabwe. We will recruit 100 individuals in Zimbabwe and 100 individuals in China.

Outcomes

We will assess the number of MSM who perform a syphilis test in each of the two pilot arms. Among those who receive testing, we will measure linkage to clinical services through administrative records at selected sites that receive training. We will compare the proportion of individuals linked to care between the two study arms.

We will supplement our primary outcome analysis with a mixed-methods evaluation of our pilot intervention:

1) We will conduct a process evaluation including both quantitative and qualitative metrics.
Quantitative metrics will include the number the number of kits distributed, the number of kits with results reported, post-testing actions (e.g., confirmatory testing) as assessed by administrative records. Final in-depth interviews will provide an opportunity to assess for both benefits and harms associated with syphilis self-testing.

2) Assessment of future large-scale trial outcome tools.
As outlined above we will supplement this with secondary outcomes that include
i) photographic confirmation of self-testing
ii) A structured questionnaire collecting data on sexual behaviours, social outcomes, self-testing usability, and HIV test uptake.

3) We will evaluate retention by the number of MSM in the original cohort who complete the six-month survey instrument, who receive a test and post-testing clinical services in each of the study arms.

Data Storage

Data and all appropriate documentation will be stored for a minimum of 5 years after the completion of the study, including the follow-up period.

10. MONITORING

10.1 RISK ASSESSMENT

This is considered a low risk study. Self-testing for HIV is a well established strategy and this study seeks to extend this approach to Syphilis. All testing kits used in the study are established, quality assured RDTs. Patients will receive standard treatment for syphilis in line with national guidelines.

10.2 MONITORING AT STUDY COORDINATION CENTRE

Data will be entered directly into an electronic database at the time of the study.

10.3 MONITORING AT LOCAL SITE

Site visits will take place at M0 (Baseline data collection) and M6 ((assessment of outcome).

11. REGULATORY ISSUES

11.1 ETHICS APPROVAL

The Study Coordination Centre has obtained approval from the LSHTM Research Ethics Committee, the SMU Dermatology Institutional Review Board (China), and the Medical Research Council of Zimbabwe Institutional Review Board.

Substantial protocol amendments will not be implemented until a favourable opinion has been granted from all ethics committee. Correspondence from both ethics committees will be maintained in the trial master file. As the duration of the study is 6 months the annual progress report will accompany the notification of the end of the study.

11.2 CONSENT

Prior to performing any study specific procedure, written informed consent will be obtained for each subject. Information sheets explaining the study will be distributed to nurses who will be trained in explaining the study. These information sheets will also be available to study participants. Written consent will be obtained in the appropriate local language on all occasions.

11.4 CONFIDENTIALITY

Subject confidentiality is strictly held in trust by the participating investigators, research staff, and the sponsoring institution and their agents. This confidentiality is extended to cover testing of biological samples and the clinical information relating to participating subjects. The study protocol, documentation, data and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party, without prior written approval of the sponsoring institution. Authorized representatives of the sponsoring institution may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records (office, clinic or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records. All evaluation forms, reports and other records that leave the site will be identified only by the Subject Identification Number (SID) to maintain subject confidentiality. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by HREC or regulatory agencies.

11.5 DATA MANAGEMENT

Data will be managed according to International Conference on Harmonisation guidelines for Good Clinical Practices. Participants will receive a unique study identification (ID) number recorded on all forms. All data will be kept confidential and accessible only to trained study staff. All consent forms and survey information will be digital only. Notes about photographic confirmation will be added to respective surveys and permanently deleted

Quantitative data: Study databases will be managed by a dedicated data manager (DM) using SOPs developed according to the Institute procedures. All data will be checked and cleaned before being updated to the main database. The databases will be regularly backed up on the local server where back-ups are maintained in the disaster recovery room and on tape media. Copies of the databases will be transferred to LSHTM using the secure server. ODK data will be uploaded directly to the LSHTM server. Paper questionnaires will be filed and stored in the archives for 5 years as per UNCST regulations.

Qualitative data: All qualitative data will be collected on digital recording devices and transported to the study sites (PZAT in Harare, SMU in Guangzhou) on the day of collection. Audio-recorded qualitative data will be transcribed, including relevant non-verbal communications. No identifying information will be provided to individuals transcribing the data and they will also sign confidentiality agreements. The interviews will be transcribed verbatim and translated into English. After translation, interview summaries will be written for each interview – these will be both a descriptive and analytic synopsis of the interview. Interview summaries will be used to come up with a provisional coding framework. Five interviews will be coded line by line on paper by more than one researcher using the coding framework. Discrepancies will be resolved by discussion. Additional codes identified through line by line coding will be added to the framework. Names and other personal identifiers will be removed from transcripts before they are entered into NVivo 10, a qualitative data storage and retrieval program. Transcripts will then be coded using the modified coding framework. Codes will be grouped and emerging themes will be identified. Analytic memos will be written for each theme.

11.6 INDEMNITY

London School of Hygiene & Tropical Medicine holds Public Liability ("negligent harm") and Clinical Trial ("non-negligent harm") insurance policies which apply to this trial.

11.7 SPONSOR

London School of Hygiene & Tropical Medicine will act as the main sponsor for this study. Delegated responsibilities will be assigned locally.

11.8 FUNDING

This study is funded as part by an MRC/DFID/Wellcome/NIHR Joint Global Health Trial Grant awarded to the investigators.

11.9 AUDITS AND INSPECTIONS

The study may be subject audit by the London School of Hygiene & Tropical Medicine under their remit as sponsor, the Study Coordination Centre and other regulatory bodies to ensure adherence to GCP.

12. TRIAL MANAGEMENT

A Trial Management Group (TMG) will be appointed and will be responsible for overseeing the progress of the trial. The day-to-day management of the trial will be co-ordinated by Joe Tucker.

All treatments in the study are being given for standard indications and the drugs have known safety profiles including in the setting of co-administration. A DSMB will therefore not be appointed.

All data will be held jointly by LSHTM and collaborators. Data will be stored on an encrypted password protected server at both LSHTM.

13. PUBLICATION POLICY

All publications and presentations relating to the study will be authorised by the Trial Management Group. The first publication of the trial results will be in the name of the Trial Management Group, if this does not conflict with the journal's policy. If there are named authors, these will include at least the trial's Chief Investigator, Statistician and Trial Coordinator. Members of the TMG and the Data Monitoring Committee will be listed and contributors will be cited by name if published in a journal where this does not conflict with the journal's policy. Authorship of parallel studies initiated outside of the Trial Management Group will be according to the individuals involved in the project but must acknowledge the contribution of the Trial Management Group and the Study Coordination Centre.

14. REFERENCES

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APPENDICES

1. Informed Consent Form
2. Study Information Sheet
3. Data Collection Forms