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A randomized controlled trial to evaluate the impact of sexual-health-clinic-based automated text message reminders on the testing of HIV and other sexually transmitted infections in men who have sex with men in China: protocol for the T2T Study

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ABSTRACT

Introduction: The frequency of screening for HIV and other sexually transmitted infections (STIs) among men who have sex with men (MSM) is still low in China.

Methods and analysis: A sexual health clinic (SHC)-based randomized controlled trial will be conducted in Guangzhou, Wuxi and Shenzhen, China, enrolling 600 MSM. Eligibility will be judged by the pre-programed iPad-based questionnaire: 1) be >=18 years of age, and 2) have had 2 or more male anal sex partners, or condomless anal sex with a casual male sex partner, or an STI history, in the past 6 months, and 3) provide a valid mobile number. Eligible men will be randomly allocated 1:1 to either Intervention Arm (with monthly text message reminding them to test for HIV/STIs) or Control Arm (without reminder). Men in both arms will complete a questionnaire onsite at enrollment and 12 months, and another questionnaire online at 6 months. Men in both arms will be tested for HIV, syphilis, anal gonorrhea/chlamydia, and penile gonorrhea/chlamydia at enrollment and 12 months. The primary outcome is the rate and frequency of HIV testing within the 12 months after enrolment. The secondary outcome is the rate of unprotected anal intercourse. An assessment of the cost-effectiveness of this intervention is also planned.

Ethics and dissemination: The study has been approved by the Ethical Review Committees of the University of New South Wales in Australia (HC16803), the Guangdong Provincial Center for Skin Disease and STI Control (GDDHLS-20160926) and Wuxi Center for Disease Control and Prevention (WXCDC2016009) in China. Study findings will be submitted to academic journals and disseminated to local health authorities.

Trial registration number: This study has been registered at the Chinese Clinical Trial Registry (http://www.chictr.org.cn/enIndex.aspx) and WHO International Clinical Trials Registry Platform (http://www.who.int/ictrp/en/), ID: ChiCTR-IPR-15006086.

Keywords

Text message service; Reminder; HIV; STI; Men who have sex with men; Sexual

health clinic

ARTICLE SUMMARY

Strengths and limitations of this study

- No study has examined the role of sexual health clinic based automated short messaging services in the testing and detection of HIV/STIs in men who have sex with men (MSM) in China.
- Findings from this study has the potential to help health authorities to develop new interventional strategies to control HIV/STIs among MSM in China.
- This intervention, from judging eligibility to sending text message reminders, is wholly automated and requires limited human input, which can be easily replicated in other sexual health clinics in China and beyond.
- Sexual behaviours and STI history during follow-up will be self-reported by participants, which may be subject to bias.
- Loss to follow-up of participants is possible in this longitudinal study.

INTRODUCTION

Men who have sex with men (MSM) in many countries are disproportionately affected by HIV and other sexually transmissible infections (STIs) such as gonorrhoea, chlamydia and syphilis [1-4]. More frequent screening for HIV and other STIs has the potential to improve detection of these largely asymptomatic infections, interrupting transmission and improving disease control [5]. Guidelines in a number of countries call for regular screening for HIV/STIs among MSM. For example, the US and Australian guidelines recommend that all MSM be screened for urethral and rectal chlamydia, pharyngeal and rectal gonorrhea, syphilis and HIV at least once a year, with 3-6 monthly screening of MSM at higher-risk for HIV/STIs transmission [6 7]. However, available data suggest that the rate of screening for these infections among MSM is much lower than recommended in many countries [8 9].

Significant increases in screening rates for gonorrhoea and chlamydia (Odds ratio (OR) range:1.4-1.9) have been demonstrated in observational studies using several different strategies: use of a computer alert on an electronic medical record [10], the introduction of clinic guidelines on STI screening [11], and short text messaging reminders for repeat STI screening [12]. Increases in syphilis testing (OR range: 2.3-21.4) were found using the following strategies: advocating regular serological screening for syphilis during routine HIV care [13]; including syphilis serology testing routinely with blood tests performed as part of HIV monitoring [14]; use of a computer alert on an electronic medical record [15]; and an electronic medical record system with a reminder to clinicians to enhance syphilis retesting following syphilis treatment [16]. A

before-and-after study in Australia using existing clinical and behavioral data of clients attending a major sexual health clinic (SHC) found that automated, computer-generated text message service (SMS) 3-monthly reminders doubled the testing rate for HIV, syphilis, gonorrhoea and chlamydia among MSM [17]. That study also demonstrated an increased detection rate for syphilis, gonorrhoea and chlamydia, but not for HIV [17]. Another before-and-after study in Australia found increased HIV/STI re-testing rates among MSM as a result of 3-6 monthly SMS reminders at a large SHC [12]. However until now there has been no randomized controlled trial to confirm these effects.

MSM in China are increasingly engaging in high risk sexual behaviors such as low rate of condom use in anal sex, multiple concurrent partnerships and drug use during sex [18]. The rates of HIV and STIs among this population are high and increasing. The estimated HIV prevalence among MSM in China increased sharply over the past decade: from 0.6% in 2003 to 8% in 2015 [19 20]. Accordingly the proportion of MSM among all people living with HIV/AIDS also climbed steadily: from 7% in 2005 to 25% in 2015 [21 22]. Many MSM in China were also infected with other STIs. A meta-analysis found that the prevalence levels of STIs among MSM in China were 6% for chlamydia, 2% for genital warts, 2% for gonorrhoea, 9% for hepatitis B, 1% for hepatitis C, 66% for human papillomavirus and 11% for herpes simplex virus-2 [23]. However the testing rate for these infections was suboptimal. A systematic review found that less than 40% of MSM in China had tested for HIV in the past year [24]. Nearly half of MSM in China had a baseline CD4+ Cell count <= 350 per mm^3 at

HIV diagnosis [25]. The rates of testing for other STIs were also low [26 27]. It is urgently needed to introduce an effective intervention that can increase testing and help achieve timely diagnosis of HIV and other STIs among MSM in China.

Our study aims to use a randomized controlled trial to evaluate the role of SHC-based automated text message services in the testing and detection of HIV and other STIs among MSM in China.

METHODS AND ANALYSIS

Overview

The proposed protocol was developed and facilitated by collaborations between experienced investigators from the Kirby Institute, the University of New South Wales (UNSW) in Sydney, Australia, Guangdong Center for Skin Disease & STI Control (GCSDSC) in Guangzhou, China, Wuxi Center for Disease Control and Prevention (CDC) in Wuxi, China, Nanshan District Center for Chronic Disease Control and Prevention (CCDC) in Shenzhen, China, and Sun Yat-sen University in Guangzhou, China. The study will randomize 600 men who have sex with men (MSM) 1:1 into Intervention Group (with reminders) and Control Group (without reminders) and evaluate the role of SHC-based automated text message services in the testing and detection of HIV/STIs among MSM. A sample size of 300 MSM in each group will provide 90% power to detect a 15.0% (from 50% to 65%) difference in the proportion of HIV testing in the past 12 months between the two groups, considering 30% of loss-to-follow-up at 12 months.

Objectives

The primary objective of this study is to determine the impact of SHC-based automated text message services on the testing and detection of HIV. The secondary objective is to determine the impact of SHC-based automated text message services on change in sexual behaviors. The additional analysis is to evaluate the costs and incremental cost-effectiveness of the intervention.

Study settings

This study will be based at the SHCs affiliated to GCSDSC, Wuxi CDC and Shenzhen Nanshan CCDC. The population in Guangzhou, Wuxi and Shenzhen was around 13, 6 and 13 million, respectively, all with per capita gross domestic product (GDP) of over USD20,000 in 2014 [28 29]. The three SHCs provide HIV/syphilis voluntary counseling and testing (VCT) and HIV/STI treatment services to over 25,000 clients annually, 10% of whom were estimated to be MSM (data not published). These three SHCs are equipped with microbiological diagnostic units and capable of timely testing and treating HIV and other STIs, including syphilis, gonorrhea, chlamydia trachomatis and genital warts.

Inclusion criteria

MSM attending the three clinics will be invited to join the study if they meet the following criteria: 1) anatomical men aged 18 years or older; 2) having over 2 male

anal sex partners, or condomless anal sex with a casual male sex partner, or an STI history, in the past 6 months; 3) possessing a mobile phone; 4) willing to provide informed consent for the collection of demographics, sexual behaviors and HIV/STI testing experiences and biological samples to test for HIV/STIs; 5) residing in a study city in the next 12 months or visiting a study city frequently enough to participate in the study; 6) willing to register testing results if they test elsewhere during the study.

Study procedures

Besides MSM attending the SHC affiliated to GCSDSC, in Guangzhou we will also work with local community clinics to refer MSM to attend the study. A study phone number will be designated to this study. This randomized controlled trial will consist of computer-assisted self-interview (CASI) and automated, computer-generated SMS reminders among 600 MSM attending the SHCs. It will be conducted over 21-24 months: 3 months of logistic preparation, 3-6 months of recruitment, 12 months of follow up and 3 months of report preparation. Detailed recruitment procedure is described in Figure 1. Over a 3-6 months recruiting period, all male clients presenting to the clinic will be given an information flyer by a receptionist who is not directly involved in the study. The flyer will include basic information about the study, including that it is a study for MSM. The receptionist will ask each male client to read the flyer and to visit the study research assistant who sits at a nearby desk, if they are interested in finding out more about the study. Those male clients who express interest in participating will see the study research assistant, who will take them to a private

clinic room where an iPad questionnaire system is installed. The study research assistant will explain what the study involves and go through the iPad-based full Participant Information and Consent Form (PICF) with potential eligible participants. Men will have time to read the PICF, to ask questions, and to decide if they will participate in the study. Men will need to click the "Agree" button to consent before completing an iPad-based questionnaire. The study research assistant will ask consented participants to complete the iPad-based questionnaire on their own, in the private room. They will be instructed that if they have any further questions, they should ask the research assistant who will be at a desk, outside of the private room. The questionnaire will collect information on sexual behaviours, HIV/STI testing behaviours and diagnosis history and alcohol/tobacco/drug use. The pre-programmed logic in the questionnaire will judge if a participant is actually eligible, based on sexual behavior variables. Those who are not eligible will be thanked and released back into the clinic waiting room for their routine clinical care. Eligible participants will provide a valid mobile phone number and then be automatically randomised into either intervention or control group, by the computer. They will then receive a text message with a code as their Study ID. When they finish the PICF and questionnaire participants will see the study research assistant who will guide them to see a doctor for bio-specimen collection, followed by routine clinical care, if necessary. Eligible MSM who opt out of the study will be recorded and asked about reasons to decline.

Detailed study procedure is described in Figure 2. We acknowledge that directly mentioning of sensitive words such as HIV and STIs in SMS reminders may lead to

the exposure of privacy of participants to others. As a result, we will avoid using these sensitive words in actual SMS reminders. Instead, in actual reminders we will use "*Little A*" to refer to "HIV", "*Little B*" to refer to "STIs", "*Health check*" to refer to "HIV/STI testing" and "*Self health check*" to refer to "HIV self-testing at home". We will clarify this in the PICF. All messages will include a withdrawal option.

For MSM in the Intervention Group, upon enrolment, they will receive Message A: "A gentle reminder: If you plan to have a health check again in the next 12 months, welcome to our center. If you do it elsewhere (including self-health check) in the next 12 months, please register the results online at the following link: ******. Every time you register we will compensate you with an electronic mobile phone credit of CNY10 (USD1.5). If you change your mobile phone number in the next 12 months please let us know." When they register online, participants need to enter the mobile phone number that was validated at enrolment and the initial of their surname to enter the questionnaire. This is designed to avoid the exposure of sensitive questions to a non participant. On the second day after enrolment, they will receive Message B: "A gentle reminder: Little A and little B are spreading rapidly and it's hard to detect by yourself. Your best protection is a regular check-up (e.g. every 3 months). If you change your mobile phone number please let us know." Starting from day 30, they will receive Message C every 30 days: "A gentle reminder: If you have not had a health check in the past 3 months please do so as soon as possible. If you change your mobile phone number please let us know." On day 190, 10 days after they receive Message C on day 180, they will receive Message D, reminding them to complete an

online survey about their sexual life and testing behaviors in the past 6 months: "A gentle reminder: please complete a survey at the following link at your earliest convenience: ******. We will compensate you with an electronic mobile phone credit of CNY50 (USD8). If you change your mobile phone number please let us know." On day 370, 10 days after they receive Message C on day 360, they will receive Message E, reminding them to complete an onsite survey about their sexual life and testing behaviours in the past 6 months: "A gentle reminder: please attend our center to complete the final survey. We will compensate you with an electronic mobile phone credit of CNY100 (USD16), together with condoms, lubricant and health booklets. If you change your mobile phone number please let us know." At enrollment and 12 months men will be tested for HIV, syphilis, urethral and anal chlamydia and gonorrohea, and examined for anogenital warts. CD4+ testing will be provided for men diagnosed with HIV. HIV/STIs will be treated as per relevant treatment guidelines in China. At 6 and 12 months men will also be asked questions about their experience of the intervention including the impact of the intervention on their everyday life, mental health, sexual health and general health (Figure 2).

MSM in the Control Group will receive Message A upon enrolment, Message D on day 190 and Message E on 370. They will not receive Messages B and C. They will complete the same questionnaire as men in the intervention group do at enrolment, 6 months and 12 months and test for above-mentioned HIV/STIs at enrolment and 12 months. They will not be asked about their experience of the intervention.

The 10 days' time gap between Messages C and D is planned to give men in both

groups enough time to attend a SHC upon receiving Message C. Besides men's mobile phone number (compulsory) we will also try to collect other contact information (optional), including email, QQ and WeChat ID (instant online messaging applications frequently used in China). At 6 and 12 months, men will be contacted with the additional contact information if they do not complete a designated survey within 7 days after Messages D and E are sent. Men who register testing information online or fill in an online questionnaire at 6 months will need to enter their mobile number to access the actual questionnaire. This is designed in case another person oversees the URL address from Message A. The process from commencing CASI to the regular dispatch of the reminders will be entirely automated, requiring no human input.

For men in both groups, at enrolment and 12 months, a study nurse will collect a swab from the anal canal to test for anal gonorrhea and chlamydia, and 5 ml of blood to test to test for HIV and syphilis. Participants will self-collect a urine sample to test for urethral gonorrhea and chlamydia. A doctor will check ano-genital warts for each participant. The HIV serologic status will be screened by ARCHITECT HIV Ag/Ab Combo assay (Abbott Laboratories, Abbott Park, Illinois, USA). Positive samples will be further screened by enzyme linked immunosorbent assay (ELISA) (Bio-Rad Laboratories, CA, USA). Samples positive for ELISA will be confirmed by the HIV-1/2 Western blot assay (HIV Blot 2.2 WB; Genelabs Diagnostics, Singapore). Confirmed HIV cases will be tested for CD4+ T Cell count. Syphilis will be screened by the toluidine red unheated serum test (TRUST) (RSbio, Shanghai, China) and

samples positive for TRUST will be confirmed by treponema pallidum particle assay (TPPA) (Fuji ReBio, Tokyo, Japan). Anal and urethral gonorrhea and chlamydia will be tested using polymerase chain reaction (PCR) (Roche Diagnostics, Shanghai, China). Ano-gential warts will be checked by a doctor with the assistance of acetic acid test.

Incentives and retention

Study participants will receive health education materials, condoms and lubricant upon completion of the CASI questionnaire at enrolment and 12 months. Participants will receive an electronic mobile phone credit of CNY50 (USD8), CNY50 (USD8) and CNY100 (USD16), upon completion of the surveys at enrolment, 6 months and 12 months. Participants who test elsewhere will receive an additional electronic mobile phone credit CNY 10 (USD 1.5) each time they register testing results online.

Statistical methods

Power/sample size

We used the following formula to calculate sample size:

$$n = \frac{(Z_\alpha \sqrt{2\overline{pq}} + Z_\beta \sqrt{p_0 q_0 + p_1 q_1})^2}{(p_1 - p_0)^2}$$

In this formula, Z_α and Z_β represent the Z boundaries under the standard normal distribution; p_1 and p_0 represents proportion of a parameter in the intervention group and control group, respectively; p equals to the average of p_1 and p_0; q=1-p. We used 2 parameters in the calculation of sample size: (a) proportion of men who have HIV

testing during the 12 months after baseline; (b) proportion of men who have condomless anal sex during the 12 months after baseline. We assumed a two-sided hypothesis test with a 5% significance level ($Z_{\alpha/2}$=1.96), a desired power of 90% (Z_{β}=1.28), and that both groups will have the same number of observations.

Using parameter (a), the rate of HIV testing in the past 12 months among MSM in Wuxi in 2014 was 50% (p_0), and this figure was expected to increase to 65% (p_1) according to a before-and-after study in Australia [17]. This resulted in a sample size of 225 in each group. Khosropour et al., retained around 70% of MSM for 12 months using bimonthly follow-up surveys through text messages [29]. We will adopt a number of strategies to minimize the loss-to-follow-up rate: educating investigators about the culture in MSM community and develop rapport with participants; verifying mobile number at enrolment; contacting participants on days 190 and 370 using various messaging softwares/apps such as WeChat, QQ, email, etc; and reasonable incentives. Considering a loss-to-follow-up rate of 30%, a sample size of 300 MSM in each group will be needed.

Analysis plan

Analyses will be performed using STATA 13.0 (College Station, TX, USA) statistical analysis software. All effects will be estimated with a 95% confidence intervals and p-values from the corresponding hypothesis tests. Statistical significance will be taken as two sided p-value less than 0.05, with no adjustment for

multiple comparisons. Characteristics of groups will be summarized at baseline and across study arms. Mean duration of study follow-up will be compared by group.

Primary analysis will compare randomized groups of MSM using an intention to treat approach. Initial analyses will be simple, unadjusted comparisons of randomised groups. If there appears to be any important imbalances between randomised groups in terms of baseline covariates, adjusted analyses will also be performed.

For the comparison of HIV/STIs testing and detection between the two groups at the end of the study: 1) we will use Cox proportional hazard models with Kaplan Meier plots and log-rank test to explore the cumulative rate of reported HIV/STIs testing and detection during the previous 12 months, comparing the two groups. Number of testing and detection of each infection will also be compared. 2) we will use Chi-square test to compare the proportion of reported HIV/STIs testing and detection during the previous 12 months before intervention with that during the 12 months after intervention, within Intervention Group. Number of testing and detection of each infection will also be compared.

For the comparison of behavioural change between the two groups at the end of the study: 1) we will use Chi-square test to compare the proportion of reported condomless anal sex during the previous 12 months between the two groups. 2) we will use rank sum test to compare the number of reported anal sex partners during the previous 12 months between the two groups. 3) we will use Chi-square test to compare the proportion of reported condomless anal sex during the previous 12

months before intervention with that during the 12 months after intervention, within Intervention Group. 4) we will use rank sum test to compare the number of reported anal sex partners during the previous 12 months before intervention with that during the 12 months after intervention, within Intervention Group.

Additional analyses

Cost and cost-effectiveness evaluation

Although some studies have assessed the cost-effectiveness of HIV testing methods among high-risk populations in some regions [31-37], whether the intervention in this study is cost-effective is unclear. As a result, the costs and incremental cost-effectiveness of the intervention compared to control will be evaluated, using standard methods of cost-effectiveness analysis [38]. Our analysis will include the costs of the self registration and SMS reminding system development and maintenance, HIV/STI testing and counseling, follow-up, and treatment. All costs will be measured from a societal perspective, and inflated to 2015 Chinese Yuan at a discounting rate of 3% annually.

Cost-Effectiveness analysis

Based on incremental cost-effectiveness analysis, we will calculate the incremental cost for one additional newly identified HIV/STI case, and one additional early HIV case, using the following formula [38]:

$$ICERij = (Ci—Cj) / （Ei - Ej）$$

Markov model based Cost-Utility analysis

We will develop a decision model to reflect when successful HIV/STI detection, follow-up, and treatment occur for a cohort of MSM with/without intervention, and then a Markov model estimating the lifecycle of MSM from entering the cohort until death, to examine the incremental cost-utility of intervention. Effectiveness is measured as quality adjusted life-years (QALYs) gained. We assume that QALYs accrues by early initiation of antiretroviral therapy (ART) following early HIV detection. According to the actual situation in China, the natural history of HIV/AIDS is categorized as the following stages: asymptomatic HIV, symptomatic HIV, AIDS and death Health states summarizes current status based on CD4+ T cell count, quality of life, ART usage and resource use. ART and CD4+ T cell count combined determines the transition probabilities and mortality rates [39 40]. The model will assess HIV status, stage transfer and its consequences among MSM with incident HIV infection on an annual basis. All the parameters used in this model will be compiled from a variety of sources, including literature review, ongoing cohort studies and investigations, surveillance data or unpublished data from Wuxi and other parts of China.

In this study, we assume that: (1) stage transition in the Markov model happens once a year, (2) once an HIV infected man receives ART, he will complete the entire treatment procedure. To account for assumptions and uncertainties of this model, we will perform one-way sensitivity analyses on all model parameters. For all the

probability variables, our ranges for sensitivity analyses represent our judgment of the variation on the basis of both the literature and discussion with experts.

Sample/data storage

All electronic questionnaires, consent forms will be stored in a password-protected computer at the information center at GCSDSC as per its common practice. The data will be stored in a format that is identifiable. This is designed to match data with individual participants in follow-up visits in this study. However, only the custodian will have access to the original data. All identifying variables, including name (a pseudonym is ok), initial of participant's surname, mobile phone number and date of birth, will be de-identified before data are transferred to a data analyst in this study. The custodian will ensure that data is stored and managed appropriately and according to the relevant privacy laws. The data custodian will only share data with researchers who are conducting HIV/STI testing related epidemiologic studies and only once these projects have received separate ethics approval from a Human Research Ethics Committee. All identifying variables, including name (a pseudonym is ok), initial of participant's surname, mobile phone number and date of birth, will be de-identified before data sharing. Bio-specimen collected at a given site will be stored at the corresponding participatory institution.

ETHICS AND DISSEMINATION

The study has been approved by the Ethical Review Committees of the University of

New South Wales in Australia (HC16803), the Guangdong Provincial Center for Skin Disease and STI Control (GDDHLS-20160926) and Wuxi Center for Disease Control and Prevention (WXCDC2016009) in China. We anticipate that the benefits of study participation will outweigh any risks, including loss of confidentiality and privacy of clinical information. Participants will benefit from frequent testing and early diagnosis of HIV/STIs and timely treatment if positive. The findings of the study will be disseminated to local and national government in China as well as the wider academic audience and public health organizations through peer-reviewed publications and international conferences.

DISCUSSION

This study protocol describes a randomized controlled trial designed to increase the testing and detection of HIV and other STIs among Chinese MSM through computer-assisted self-interview and automated computer generated reminders. Firstly, we seek to develop a platform requiring limited investment and human power that could be easily replicated and deployed in other SHCs in China and beyond. As such, one of the challenges in designing the intervention was the acceptance of it among target population-MSM in China-a population that has long been marginalized and discriminated against. Fortunately in our unpublished pre-trial study, almost 80% of MSM in the community were willing to take such an intervention. It is estimated that this rate would be even higher among MSM

attending SHCs. Other key challenges to this study include the need to sustain the motivation of clinic staff to participate in the study while addressing the multiple competing health priorities. Secondly, we will be able to understand MSM with what characteristics are more likely to take this intervention and barriers that prevent other MSM from taking this intervention. This will help develop an intervention that is contextualized and tailored to the characteristics of MSM. Thirdly, if successful, this intervention with high potential cost-effectiveness will contribute to the compilation of the fabric of quality SHCs and health providers that will eventually be readily available to MSM at their finger tips. This will greatly encourage and facilitate them to test for HIV/STIs on a more frequent basis. Lastly, results from this study may facilitate the development of proactive interventions strategies targeting other at-risk populations, such as female sex workers and their clients, and drug users, etc. to increase the testing and detection of HIV and other STIs and hence prevent the transmission of these infections.

This intervention has its limitations: Firstly, the 12-months research period is a long commitment for MSM as many of them are quite mobile. The retention rate could be compromised by 12 months. To tackle this problem we will verify participants' mobile phone number at enrolment and remind them to update their mobile number every 30 days. Additionally we will also use other contact information reported by participants to achieve the highest possible retention rate. Secondly, men could forget to register testing experience from other venues. To tackle this problem, we will remind them to do this in Message A at enrolment.

Because a similar reminder during the study would potentially bring about contamination to the intervention, we will not send further reminders. Thirdly, as this intervention will be conducted in metropolitan cities, the results may not apply to that in other settings.

In summary the knowledge gained from this study may be used to design similar protocols with a higher number of participants and appropriate intervention strategies to reduce the burden of HIV and other STIs among MSM, a population who is heavily burdened by these infections. Additionally, if the results are positive, we will scale up this practice in more SHCs across China.

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Authors' contribution

Huachun Zou and Xiaojun Meng initiated this research plan and designed this protocol with Bin Yang and Andrew Grulich consulting on ethics and feasibility of the research. Zhenzhou Luo, Tianjian Jia, Xuan Zhang, Yi Ding and Ligang Yang provided expertise on recruitment and sample collection and will supervise these aspects at the three study clinics. Jinmei Huang, Shujie Huang and Heping Zheng provided expertise on sample testing and storage. Weiying Chen helped with the design of questionnaire and recruitment methods.

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Competing interests

All authors declare no competing interests.

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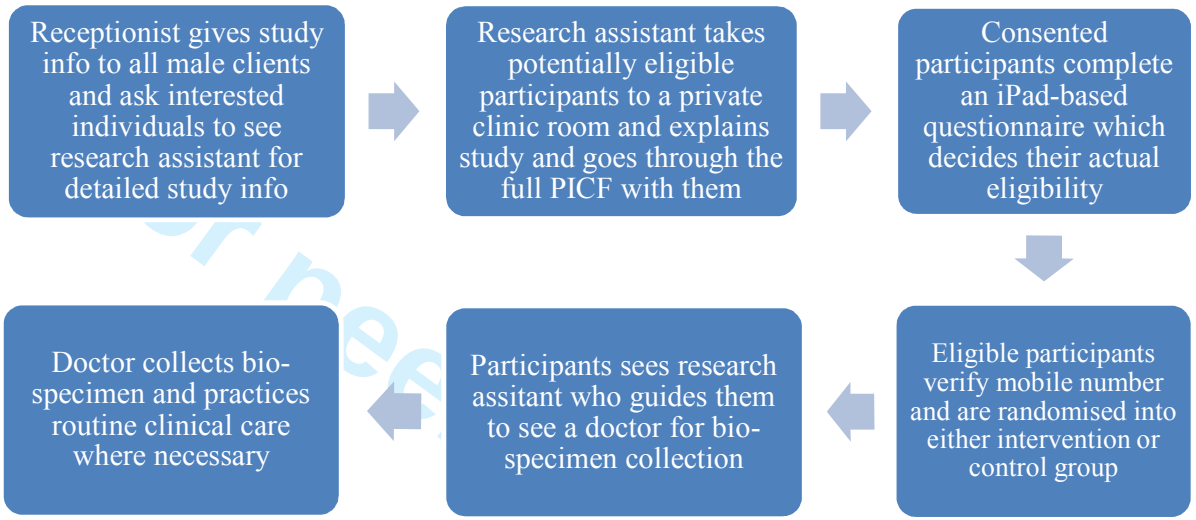

Figure 1. Flow chart of recruitment

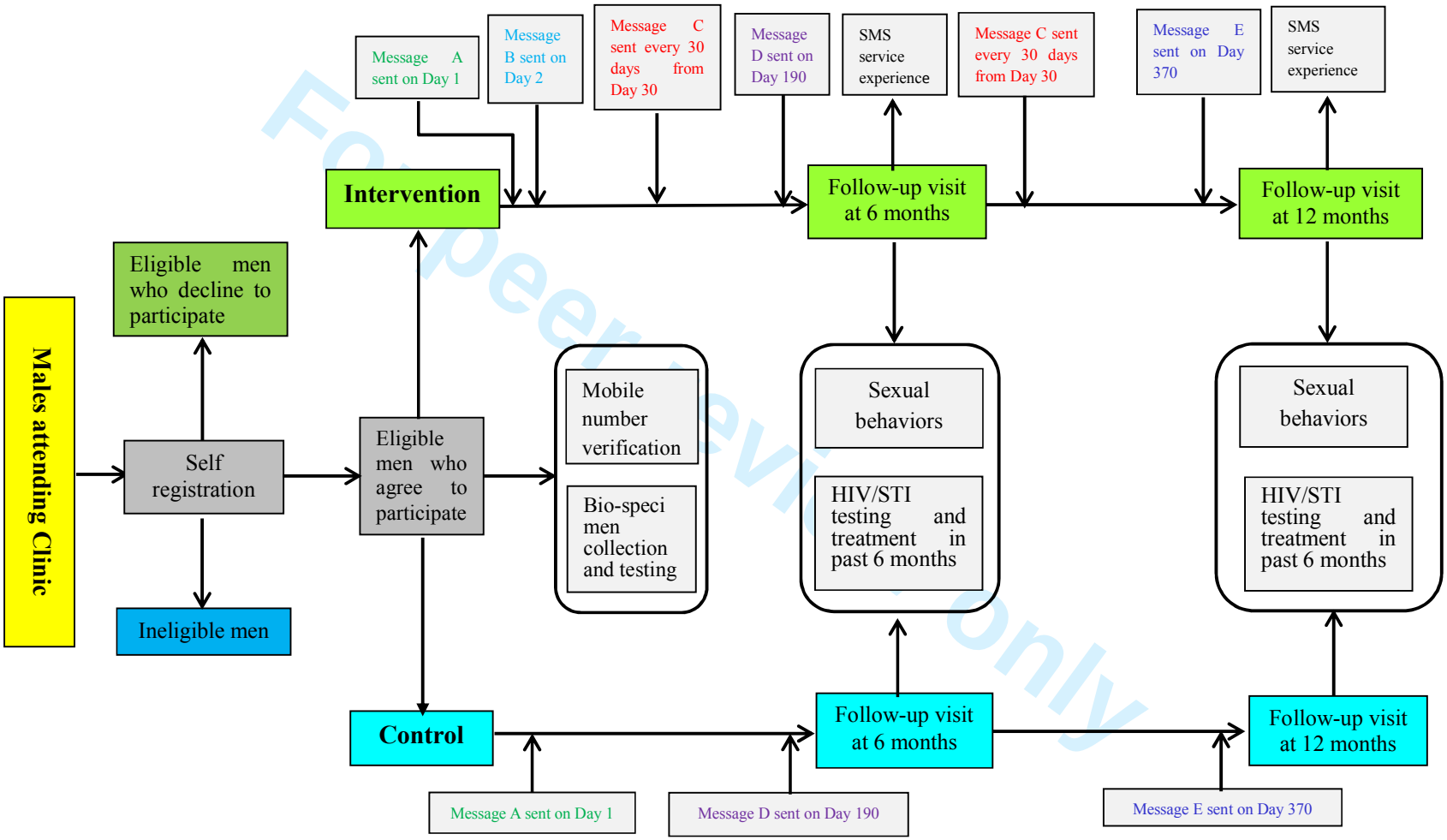

Figure 2. Flowchart of study procedure

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3-5
	2b	Specific objectives or hypotheses	5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	N/A
Participants	4a	Eligibility criteria for participants	6-7
	4b	Settings and locations where the data were collected	6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	9-11
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	8
	6b	Any changes to trial outcomes after the trial commenced, with reasons	N/A
Sample size	7a	How sample size was determined	12-13
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	8
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	8
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	8
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	8
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	8

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	N/A
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	13-14
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	15-16
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	N/A
	13b	For each group, losses and exclusions after randomisation, together with reasons	N/A
Recruitment	14a	Dates defining the periods of recruitment and follow-up	7
	14b	Why the trial ended or was stopped	8
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	N/A
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	N/A
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	N/A
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	N/A
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	N/A
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	12
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	19
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	18-19
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	19
Other information			
Registration	23	Registration number and name of trial registry	2
Protocol	24	Where the full trial protocol can be accessed, if available	N/A
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	20-21

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ Open

A randomized controlled trial to evaluate the impact of sexual-health-clinic-based automated text message reminders on the testing of HIV and other sexually transmitted infections in men who have sex with men in China: protocol for the T2T Study

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Secondary Subject Heading:	Health services research, Health policy, Sexual health
Keywords:	Text message service, Reminder, HIV, STI, Men who have sex with men, Sexual health clinic

A randomized controlled trial to evaluate the impact of sexual-health-clinic-based automated text message reminders on the testing of HIV and other sexually transmitted infections in men who have sex with men in China: protocol for the T2T Study

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ABSTRACT

Introduction: The frequency of screening for HIV and other sexually transmitted infections (STIs) among men who have sex with men (MSM) is still low in China.

Methods and analysis: A sexual health clinic (SHC)-based randomized controlled trial will be conducted in Guangzhou, Wuxi and Shenzhen, China, enrolling 600 MSM. Eligibility will be judged by the pre-programed iPad-based questionnaire: 1) be >=18 years of age, and 2) have had 2 or more male anal sex partners, or condomless anal sex with a casual male sex partner, or an STI history, in the past 6 months, and 3) provide a valid mobile number. Eligible men will be randomly allocated 1:1 to either Intervention Arm (with monthly text message reminding them to test for HIV/STIs) or Control Arm (without reminder). Men in both arms will complete a questionnaire onsite at enrollment and 12 months, and another questionnaire online at 6 months. Men in both arms will be tested for HIV, syphilis, anal gonorrhea/chlamydia, and penile gonorrhea/chlamydia at enrollment and 12 months. The primary outcome is the rate and frequency of HIV testing within the 12 months after enrolment. The secondary outcome is the rate of unprotected anal intercourse. An assessment of the cost-effectiveness of this intervention is also planned.

Ethics and dissemination: The study has been approved by the Ethical Review Committees of the University of New South Wales in Australia (HC16803), the Guangdong Provincial Center for Skin Disease and STI Control (GDDHLS-20160926) and Wuxi Center for Disease Control and Prevention (WXCDC2016009) in China. Study findings will be submitted to academic journals and disseminated to local health authorities.

Trial registration number: This study has been registered at the Chinese Clinical Trial Registry (http://www.chictr.org.cn/enIndex.aspx) and WHO International Clinical Trials Registry Platform (http://www.who.int/ictrp/en/), ID: ChiCTR-IPR-15006086.

Keywords

Text message service; Reminder; HIV; STI; Men who have sex with men; Sexual

health clinic

ARTICLE SUMMARY

Strengths and limitations of this study

- No study has examined the role of sexual health clinic based automated short messaging services in the testing and detection of HIV/STIs in men who have sex with men (MSM) in China.
- Findings from this study has the potential to help health authorities to develop new interventional strategies to control HIV/STIs among MSM in China.
- This intervention, from judging eligibility to sending text message reminders, is wholly automated and requires limited human input, which can be easily replicated in other sexual health clinics in China and beyond.
- Sexual behaviours and STI history during follow-up will be self-reported by participants, which may be subject to bias.
- Loss to follow-up of participants is possible in this longitudinal study.

INTRODUCTION

Men who have sex with men (MSM) in many countries are disproportionately affected by HIV and other sexually transmissible infections (STIs) such as gonorrhoea, chlamydia and syphilis[1-4]. More frequent screening for HIV and other STIs has the potential to improve detection of these largely asymptomatic infections, interrupting transmission and improving disease control [5]. Guidelines in a number of countries call for regular screening for HIV/STIs among MSM. For example, the US and Australian guidelines recommend that all MSM be screened for urethral and rectal chlamydia, pharyngeal and rectal gonorrhea, syphilis and HIV at least once a year, with 3-6 monthly screening of MSM at higher-risk for HIV/STIs transmission [6 7]. However, available data suggest that the rate of screening for these infections among MSM is much lower than recommended in many countries[8 9].

Significant increases in screening rates for gonorrhoea and chlamydia (Odds ratio (OR) range:1.4-1.9) have been demonstrated in observational studies using several different strategies: use of a computer alert on an electronic medical record [10], the introduction of clinic guidelines on STI screening [11], and short text messaging reminders for repeat STI screening [12 13]. Increases in syphilis testing (OR range: 2.3-21.4) were found using the following strategies: advocating regular serological screening for syphilis during routine HIV care [14]; including syphilis serology testing routinely with blood tests performed as part of HIV monitoring [15]; use of a computer alert on an electronic medical record [16]; and an electronic medical record system with a reminder to clinicians to enhance syphilis retesting following syphilis treatment [17]. A

before-and-after study in Australia using existing clinical and behavioral data of clients attending a major sexual health clinic (SHC) found that automated, computer-generated text message service (SMS) 3-monthly reminders doubled the testing rate for HIV, syphilis, gonorrhoea and chlamydia among MSM [18]. That study also demonstrated an increased detection rate for syphilis, gonorrhoea and chlamydia, but not for HIV [18]. Another before-and-after study in Australia found increased HIV/STI re-testing rates among MSM as a result of 3-6 monthly SMS reminders at a large SHC [12]. However until now there has been no randomized controlled trial to confirm these effects.

MSM in China are increasingly engaging in high risk sexual behaviors such as low rate of condom use in anal sex, multiple concurrent partnerships and drug use during sex [19]. The rates of HIV and STIs among this population are high and increasing. The estimated HIV prevalence among MSM in China increased sharply over the past decade: from 0.6% in 2003 to 8% in 2015 [20 21]. Accordingly the proportion of MSM among all people living with HIV/AIDS also climbed steadily: from 7% in 2005 to 25% in 2015 [22 23]. Many MSM in China were also infected with other STIs. A meta-analysis found that the prevalence levels of STIs among MSM in China were 6% for chlamydia, 2% for genital warts, 2% for gonorrhoea, 9% for hepatitis B, 1% for hepatitis C, 66% for human papillomavirus and 11% for herpes simplex virus-2 [24]. However the testing rate for these infections was suboptimal. A systematic review found that less than 40% of MSM in China had tested for HIV in the past year [25]. Nearly half of MSM in China had a baseline CD4+ Cell count <= 350 per mm^3 at

HIV diagnosis [26]. The rates of testing for other STIs were also low [27 28]. It is urgently needed to introduce an effective intervention that can increase testing and help achieve timely diagnosis of HIV and other STIs among MSM in China.

Our study aims to use a randomized controlled trial to evaluate the role of SHC-based automated text message services in the testing and detection of HIV and other STIs among MSM in China.

METHODS AND ANALYSIS

Overview

The proposed protocol (dated December 8, 2016) was developed and facilitated by collaborations between experienced investigators from the Kirby Institute, the University of New South Wales (UNSW) in Sydney, Australia, Dermatology Hospital of Southern Medical University (DHSMU) in Guangzhou, China, Wuxi Center for Disease Control and Prevention (CDC) in Wuxi, China, Nanshan District Center for Chronic Disease Control and Prevention (CCDC) in Shenzhen, China, and Sun Yat-sen University in Guangzhou, China. The study will randomize 600 men who have sex with men (MSM) 1:1 into Intervention Group (with reminders) and Control Group (without reminders) and evaluate the role of SHC-based automated text message services in the testing and detection of HIV/STIs among MSM. A sample size of 300 MSM in each group will provide 90% power to detect a 15.0% (from 50% to 65%) difference in the proportion of HIV testing in the past 12 months between the two groups, considering 30% of loss-to-follow-up at 12 months.

Objectives

The primary objective of this study is to determine the impact of SHC-based automated text message services on the testing and detection of HIV. The secondary objective is to determine the impact of SHC-based automated text message services on the change in sexual behaviors. The additional analysis is to evaluate the costs and incremental cost-effectiveness of the intervention.

Study settings

This study will be based at the SHCs affiliated to DHSMU, Wuxi CDC and Shenzhen Nanshan CCDC. The population in Guangzhou, Wuxi and Shenzhen was around 13, 6 and 13 million, respectively, all with per capita gross domestic product (GDP) of over USD20,000 in 2014 [29-31]. The three SHCs provide HIV/syphilis voluntary counseling and testing (VCT) and HIV/STI treatment services to over 25,000 clients annually, 10% of whom were estimated to be MSM (data not published). These three SHCs are equipped with microbiological diagnostic units and capable of timely testing and treating HIV and other STIs, including syphilis, gonorrhea, chlamydia trachomatis and genital warts.

Inclusion criteria

MSM attending the three clinics will be invited to join the study if they meet the following criteria: 1) anatomical men aged 18 years or older; 2) having over 2 male

anal sex partners, or condomless anal sex with a casual male sex partner, or an STI history including gonorrhea, syphilis, anogenital warts, genital herpes and chlamydia trachomatis, in the past 6 months; 3) possessing a mobile phone; 4) willing to provide informed consent for the collection of demographics, sexual behaviors and HIV/STI testing experiences and biological samples to test for HIV/STIs; 5) residing in a study city in the next 12 months or visiting a study city frequently enough to participate in the study; 6) willing to register testing results if they test elsewhere during the study.

Exclusion criteria

MSM who meets one or more criteria listed below will be excluded: 1) has psychiatric illnesses; 2) unable to read or use the iPad questionnaire; 3) does not speak or read the Chinese languages

Study procedures

Besides MSM attending the SHC affiliated to DHSMU, in Guangzhou we will also work with local community clinics to refer MSM to attend the study. A study phone number will be designated to this study. This randomized controlled trial will consist of computer-assisted self-interview (CASI) and automated, computer-generated SMS reminders among 600 MSM attending the SHCs. It will be conducted over 21-24 months: 3 months of logistic preparation, 3-6 months of recruitment, 12 months of follow up and 3 months of report preparation. Detailed recruitment procedure is described in Figure 1. Over a 3-6 months recruiting period, all male clients presenting

to the clinic will be given an information flyer by a receptionist who is not directly involved in the study. The flyer will include basic information about the study, including that it is a study for MSM. The receptionist will ask each male client to read the flyer and to visit the study research assistant who sits at a nearby desk, if they are interested in finding out more about the study. Those male clients who express interest in participating will see the study research assistant, who will take them to a private clinic room where an iPad questionnaire system is installed. The study research assistant will explain what the study involves and go through the iPad-based full Participant Information and Consent Form (PICF) with potential eligible participants. Men will have time to read the PICF, to ask questions, and to decide if they will participate in the study. Men will need to click the "Agree" button to consent before completing an iPad-based questionnaire. The study research assistant will ask consented participants to complete the iPad-based questionnaire on their own, in the private room. They will be instructed that if they have any further questions, they should ask the research assistant who will be at a desk, outside of the private room. The questionnaire will collect information on sexual behaviours, HIV/STI testing behaviours and diagnosis history and alcohol/tobacco/drug use. The pre-programmed logic in the questionnaire will judge if a participant is actually eligible, based on sexual behavior variables. Those who are not eligible will be thanked and released back into the clinic waiting room for their routine clinical care. Eligible participants will provide a valid mobile phone number and then be automatically randomised into either intervention or control group, by the computer. They will then receive a text

message with a code as their Study ID. When they finish the PICF and questionnaire participants will see the study research assistant who will guide them to see a doctor for bio-specimen collection, followed by routine clinical care, if necessary. Eligible MSM who opt out of the study will be recorded and asked about reasons to decline.

Detailed study procedure is described in Figure 2. We acknowledge that directly mentioning of sensitive words such as HIV and STIs in SMS reminders may lead to the exposure of privacy of participants to others. As a result, we will avoid using these sensitive words in actual SMS reminders. Instead, in actual reminders we will use "*Little A*" to refer to "HIV", "*Little B*" to refer to "STIs", "*Health check*" to refer to "HIV/STI testing", "*Self health check*" to refer to "HIV self-testing at home", and "health kit" to refer to "condoms/lubes/MSM health manuals". We will clarify this in the PICF. All messages will include a withdrawal option.

For MSM in the Intervention Group, upon enrolment, they will receive Message A: "A gentle reminder: If you plan to have a health check again in the next 12 months, welcome to our center. If you do it elsewhere (including self-health check) in the next 12 months, please register the results online at the following link: ******. Every time you register we will compensate you with an electronic mobile phone credit of CNY10 (USD1.5). If you change your mobile phone number in the next 12 months please let us know." When they register online, participants need to enter the mobile phone number that was validated at enrolment and the initial of their surname to enter the questionnaire. This is designed to avoid the exposure of sensitive questions to a non participant. On the second day after enrolment, they will receive Message B: "A

gentle reminder: Little A and little B are spreading rapidly and it's hard to detect by yourself. Your best protection is a regular check-up (e.g. every 3 months). If you change your mobile phone number please let us know." Starting from day 30, they will receive Message C every 30 days: "A gentle reminder: If you have not had a health check in the past 3 months please do so as soon as possible. If you change your mobile phone number please let us know." On day 190, 10 days after they receive Message C on day 180, they will receive Message D, reminding them to complete an online survey about their sexual life and testing behaviors in the past 6 months: "A gentle reminder: please complete a survey at the following link at your earliest convenience: ******. We will compensate you with an electronic mobile phone credit of CNY50 (USD8). If you change your mobile phone number please let us know." On day 370, 10 days after they receive Message C on day 360, they will receive Message E, reminding them to complete an onsite survey about their sexual life and testing behaviours in the past 6 months: "A gentle reminder: please attend our center to complete the final survey. We will compensate you with an electronic mobile phone credit of CNY100 (USD16), together with a health kit. If you change your mobile phone number please let us know." At enrollment and 12 months men will be tested for HIV, syphilis, urethral and anal chlamydia and gonorrohea, and examined for anogenital warts. CD4+ testing will be provided for men diagnosed with HIV. HIV/STIs will be treated as per relevant treatment guidelines in China. At 6 and 12 months men will also be asked questions about their experience of the intervention including the impact of the intervention on their everyday life, mental health, sexual

health and general health (Figure 2).

MSM in the Control Group will receive Message A upon enrolment, Message D on day 190 and Message E on 370. They will not receive Messages B and C. They will complete the same questionnaire as men in the intervention group do at enrolment, 6 months and 12 months and test for above-mentioned HIV/STIs at enrolment and 12 months. They will not be asked about their experience of the intervention.

The 10 days' time gap between Messages C and D is planned to give men in both groups enough time to attend a SHC upon receiving Message C. Besides men's mobile phone number (compulsory) we will also try to collect other contact information (optional), including email, QQ and WeChat ID (instant online messaging applications frequently used in China). At 6 and 12 months, men will be contacted with the additional contact information if they do not complete a designated survey within 7 days after Messages D and E are sent. Men who register testing information online or fill in an online questionnaire at 6 months will need to enter their mobile number to access the actual questionnaire. This is designed in case another person oversees the URL address from Message A. The process from commencing CASI to the regular dispatch of the reminders will be entirely automated, requiring no human input.

For men in both groups, at enrolment and 12 months, a study nurse will collect a swab from the anal canal to test for anal gonorrhea and chlamydia, and 5 ml of blood to test to test for HIV and syphilis. Participants will self-collect a urine sample to test for urethral gonorrhea and chlamydia. A doctor will check ano-genital warts for each

participant. The HIV serologic status will be screened by ARCHITECT HIV Ag/Ab Combo assay (Abbott Laboratories, Abbott Park, Illinois, USA). Positive samples will be further screened by enzyme linked immunosorbent assay (ELISA) (Bio-Rad Laboratories, CA, USA). Samples positive for ELISA will be confirmed by the HIV-1/2 Western blot assay (HIV Blot 2.2 WB; Genelabs Diagnostics, Singapore). Confirmed HIV cases will be tested for CD4+ T Cell count. Syphilis will be screened by the toluidine red unheated serum test (TRUST) (RSbio, Shanghai, China) and samples positive for TRUST will be confirmed by treponema pallidum particle assay (TPPA) (Fuji ReBio, Tokyo, Japan). Anal and urethral gonorrhea and chlamydia will be tested using polymerase chain reaction (PCR) (Roche Diagnostics, Shanghai, China). Ano-gential warts will be checked by a doctor with the assistance of acetic acid test.

Incentives and retention

Study participants will receive health education materials, condoms and lubricant upon completion of the CASI questionnaire at enrolment and 12 months. Participants will receive an electronic mobile phone credit of CNY50 (USD8), CNY50 (USD8) and CNY100 (USD16), upon completion of the surveys at enrolment, 6 months and 12 months. Participants who test elsewhere will receive an additional electronic mobile phone credit CNY 10 (USD 1.5) each time they register testing results online.

Statistical methods

Power/sample size

We used the following formula to calculate sample size:

$$n = \frac{(Z_\alpha \sqrt{2\overline{pq}} + Z_\beta \sqrt{p_0 q_0 + p_1 q_1})^2}{(p_1 - p_0)^2}$$

In this formula, Z_α and Z_β represent the Z boundaries under the standard normal distribution; p_1 and p_0 represents proportion of a parameter in the intervention group and control group, respectively; p equals to the average of p_1 and p_0; q=1-p. We used 2 parameters in the calculation of sample size: (a) proportion of men who have HIV testing during the 12 months after baseline; (b) proportion of men who have condomless anal sex during the 12 months after baseline. We assumed a two-sided hypothesis test with a 5% significance level ($Z_{\alpha/2}$=1.96), a desired power of 90% (Z_β=1.28), and that both groups will have the same number of observations.

Using parameter (a), the rate of HIV testing in the past 12 months among MSM in Wuxi in 2014 was 50% (p_0), and this figure was expected to increase to 65% (p_1) according to a before-and-after study in Australia [18]. This resulted in a sample size of 225 in each group. Khosropour et al., retained around 70% of MSM for 12 months using bimonthly follow-up surveys through text messages [30]. We will adopt a number of strategies to minimize the loss-to-follow-up rate: educating investigators about the culture in MSM community and develop rapport with participants; verifying mobile number at enrolment; contacting participants on days 190 and 370 using various messaging softwares/apps such as WeChat, QQ, email, etc; and reasonable incentives. Considering a loss-to-follow-up rate of 30%, a sample size of 300 MSM in each group will be needed.

Analysis plan

Analyses will be performed using STATA 13.0 (College Station, TX, USA) statistical analysis software. All effects will be estimated with a 95% confidence intervals and p-values from the corresponding hypothesis tests. Statistical significance will be taken as two sided p-value less than 0.05, with no adjustment for multiple comparisons. Characteristics of groups will be summarized at baseline and across study arms. Mean duration of study follow-up will be compared by group.

Primary analysis will compare randomized groups of MSM using an intention to treat approach. Initial analyses will be simple, unadjusted comparisons of randomised groups. If there appears to be any important imbalances between randomised groups in terms of baseline covariates, adjusted analyses will also be performed.

For the comparison of HIV/STIs testing and detection between the two groups at the end of the study: 1) we will use Cox proportional hazard models with Kaplan Meier plots and log-rank test to explore the cumulative rate of reported HIV/STIs testing and detection during the previous 12 months, comparing the two groups. Number of testing and detection of each infection will also be compared. 2) we will use Chi-square test to compare the proportion of reported HIV/STIs testing and detection during the previous 12 months before intervention with that during the 12 months after intervention, within Intervention Group. Number of testing and detection of each infection will also be compared.

For the comparison of behavioural change between the two groups at the end of the study: 1) we will use Chi-square test to compare the proportion of reported condomless anal sex during the previous 12 months between the two groups. 2) we will use rank sum test to compare the number of reported anal sex partners during the previous 12 months between the two groups. 3) we will use Chi-square test to compare the proportion of reported condomless anal sex during the previous 12 months before intervention with that during the 12 months after intervention, within Intervention Group. 4) we will use rank sum test to compare the number of reported anal sex partners during the previous 12 months before intervention with that during the 12 months after intervention, within Intervention Group.

Additional analyses

Cost and cost-effectiveness evaluation

Although some studies have assessed the cost-effectiveness of HIV testing methods among high-risk populations in some regions [32-38], whether the intervention in this study is cost-effective is unclear. As a result, the costs and incremental cost-effectiveness of the intervention compared to control will be evaluated, using standard methods of cost-effectiveness analysis [39]. Our analysis will include the costs of the self-registration and SMS reminding system development and maintenance, HIV/STI testing and counseling, follow-up, and treatment. All costs will be measured from a societal perspective, and inflated to 2015 Chinese Yuan at a discounting rate of 3% annually.

Cost-Effectiveness analysis

Based on incremental cost-effectiveness analysis, we will calculate the incremental cost for one additional newly identified HIV/STI case, and one additional early HIV case, using the following formula [39]:

ICERij = (Ci—Cj) / （Ei - Ej）

Markov model based Cost-Utility analysis

We will develop a decision model to reflect when successful HIV/STI detection, follow-up, and treatment occur for a cohort of MSM with/without intervention, and then a Markov model estimating the lifecycle of MSM from entering the cohort until death, to examine the incremental cost-utility of intervention. Effectiveness is measured as quality adjusted life-years (QALYs) gained. We assume that QALYs accrues by early initiation of antiretroviral therapy (ART) following early HIV detection. According to the actual situation in China, the natural history of HIV/AIDS is categorized as the following stages: asymptomatic HIV, symptomatic HIV, AIDS and death Health states summarizes current status based on CD4+ T cell count, quality of life, ART usage and resource use. ART and CD4+ T cell count combined determines the transition probabilities and mortality rates [40 41]. The model will assess HIV status, stage transfer and its consequences among MSM with incident HIV infection on an annual basis. All the parameters used in this model will be compiled from a variety of sources, including literature review, ongoing cohort

studies and investigations, surveillance data or unpublished data from Wuxi and other parts of China.

In this study, we assume that: (1) stage transition in the Markov model happens once a year, (2) once an HIV infected man receives ART, he will complete the entire treatment procedure. To account for assumptions and uncertainties of this model, we will perform one-way sensitivity analyses on all model parameters. For all the probability variables, our ranges for sensitivity analyses represent our judgment of the variation on the basis of both the literature and discussion with experts.

Sample/data storage

All electronic questionnaires, consent forms will be stored in a password-protected computer at the information center at DHSMU as per its common practice. The data will be stored in a format that is identifiable. This is designed to match data with individual participants in follow-up visits in this study. However, only the custodian will have access to the original data. All identifying variables, including name (a pseudonym is ok), initial of participant's surname, mobile phone number and date of birth, will be de-identified before data are transferred to a data analyst in this study. The custodian will ensure that data is stored and managed appropriately and according to the relevant privacy laws. The data custodian will only share data with researchers who are conducting HIV/STI testing related epidemiologic studies and only once these projects have received separate ethics approval from a Human Research Ethics Committee. All identifying variables, including name (a pseudonym

is ok), initial of participant's surname, mobile phone number and date of birth, will be de-identified before data sharing. Bio-specimen collected at a given site will be stored at the corresponding participatory institution.

ETHICS AND DISSEMINATION

The study has been approved by the Ethical Review Committees of the University of New South Wales in Australia (HC16803), the Dermatology Hospital of Southern Medical University (GDDHLS-20160926) and Wuxi Center for Disease Control and Prevention (WXCDC2016009) in China. We anticipate that the benefits of study participation will outweigh any risks, including loss of confidentiality and privacy of clinical information. Participants will benefit from frequent testing and early diagnosis of HIV/STIs and timely treatment if positive. The findings of the study will be disseminated to local and national government in China as well as the wider academic audience and public health organizations through peer-reviewed publications and international conferences.

DISCUSSION

This study protocol describes a randomized controlled trial designed to increase the testing and detection of HIV and other STIs among Chinese MSM through computer-assisted self-interview and automated computer generated reminders. Firstly, we seek to develop a platform requiring limited investment and human power that could be easily replicated and deployed in other SHCs in China and

beyond. As such, one of the challenges in designing the intervention was the acceptance of it among target population-MSM in China-a population that has long been marginalized and discriminated against. Fortunately in our unpublished pre-trial study, almost 80% of MSM in the community were willing to take such an intervention. It is estimated that this rate would be even higher among MSM attending SHCs. Other key challenges to this study include the need to sustain the motivation of clinic staff to participate in the study while addressing the multiple competing health priorities. Secondly, we will be able to understand MSM with what characteristics are more likely to take this intervention and barriers that prevent other MSM from taking this intervention. This will help develop an intervention that is contextualized and tailored to the characteristics of MSM. Thirdly, if successful, this intervention with high potential cost-effectiveness will contribute to the compilation of the fabric of quality SHCs and health providers that will eventually be readily available to MSM at their finger tips. This will greatly encourage and facilitate them to test for HIV/STIs on a more frequent basis. Lastly, results from this study may facilitate the development of proactive interventions strategies targeting other at-risk populations, such as female sex workers and their clients, and drug users, etc. to increase the testing and detection of HIV and other STIs and hence prevent the transmission of these infections.

This intervention has its limitations: Firstly, the 12-months research period is a long commitment for MSM as many of them are quite mobile. The retention rate could be compromised by 12 months. To tackle this problem we will verify

participants' mobile phone number at enrolment and remind them to update their mobile number every 30 days. Additionally we will also use other contact information reported by participants to achieve the highest possible retention rate. Secondly, men could forget to register testing experience from other venues. To tackle this problem, we will remind them to do this in Message A at enrolment. Because a similar reminder during the study would potentially bring about contamination to the intervention, we will not send further reminders. Thirdly, as this intervention will be conducted in metropolitan cities, the results may not apply to that in other settings.

In summary the knowledge gained from this study may be used to design similar protocols with a higher number of participants and appropriate intervention strategies to reduce the burden of HIV and other STIs among MSM, a population who is heavily burdened by these infections. Additionally, if the results are positive, we will scale up this practice in more SHCs across China.

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Authors' contribution

Huachun Zou and Xiaojun Meng initiated this research plan and designed this protocol with Bin Yang and Andrew Grulich consulting on ethics and feasibility of

the research. Zhenzhou Luo, Tianjian Jia, Xuan Zhang, Yi Ding and Ligang Yang provided expertise on recruitment and sample collection and will supervise these aspects at the three study clinics. Jinmei Huang, Shujie Huang and Heping Zheng provided expertise on sample testing and storage. Weiying Chen helped with the design of questionnaire and recruitment methods.

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Competing interests

All authors declare no competing interests.

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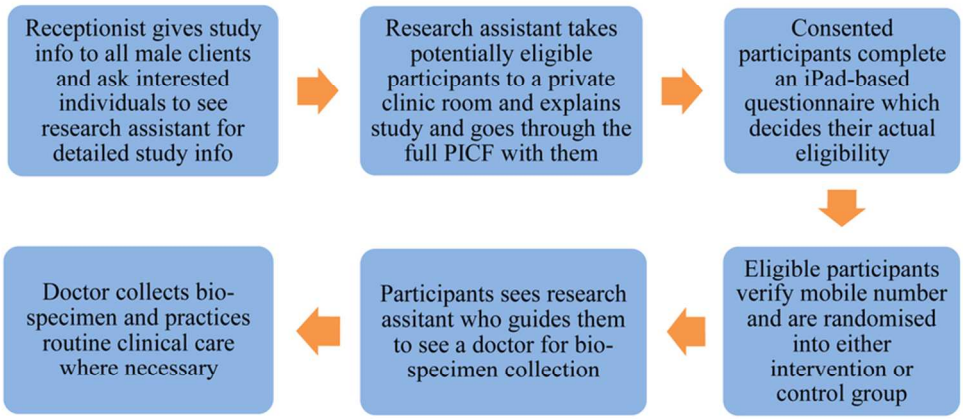

Figure 1. Flow chart of recruitment

Flow chart of recruitment

83x40mm (300 x 300 DPI)

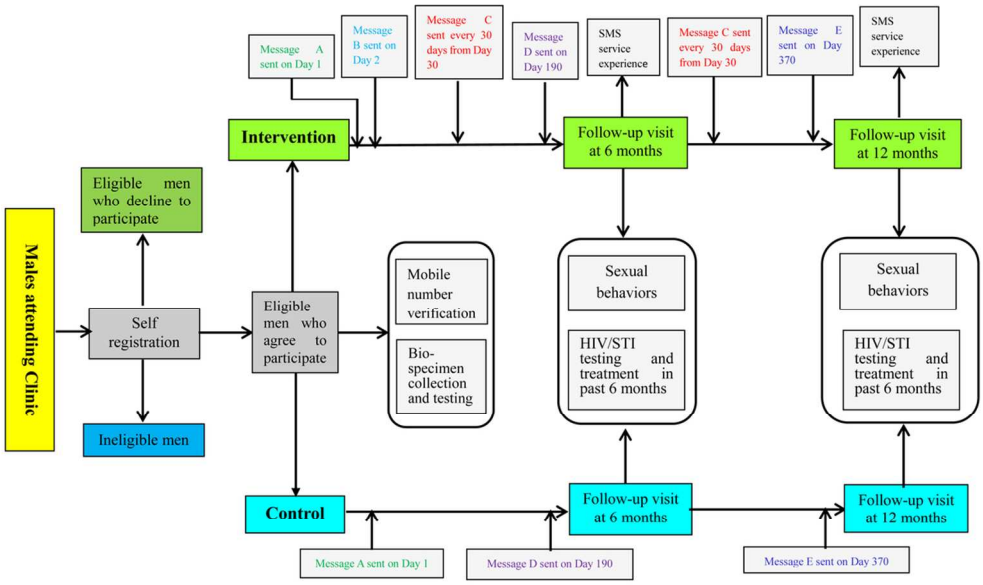

Figure 2. Flowchart of study procedure

Flowchart of study procedure

109x68mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Reported on page No
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	3	Date and version identifier	6
Funding	4	Sources and types of financial, material, and other support	21
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	21
	5b	Name and contact information for the trial sponsor	21
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	21

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-6
	6b	Explanation for choice of comparators	4-6
Objectives	7	Specific objectives or hypotheses	7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10-11

	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	13
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	14-17
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	8
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	13-14
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	8

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	9
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	17-18
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	17-18

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	17-18
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	15
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	16-17
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	15
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	17-18
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	18
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	N/A
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	18

Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	19
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8-9
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	27
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	17-18
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	21
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	18
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	18
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	18

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	27
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	12

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

Sample patient information and consent form

1. **What is the research study about?**
Over 7% of men who have sex with men (MSM) in China have been infected with HIV, with over 10% infected with syphilis and over 30% infected with gonorrhea, condyloma and other sexually transmitted infections (STIs). You are cordially invited to a participate in a study about HIV/STI testing, jointly conducted by Guangdong Provincial Center for Skin Disease and STI Control, Wuxi Municipal Center for Disease Control and Prevention, Shenzhen Nanshan Center for Chronic Disease Control and Prevention, Sun Yat-sen University and the University of New South Wales. This study aims to understand if automated short message service (SMS) reminders can lead to frequent testing and early diagnosis/treatment among MSM. Your participation will help us to improve HIV prevention strategy for the MSM community.

If you are eligible and willing to participate in this study, you will need to provide a valid phone number that will be verified by a code sent to you via SMS. Participants will be randomly allocated into two groups: one group will receive a testing reminder via SMS every 30 days, while the other group will not receive any reminder.

2. **Inclusion/Exclusion Criteria**
Before you decide to participate in this research project, we need to ensure that it is ok for you to take part. If you have ever had a male sex partner you may be eligible to participate in the study. Your eligibility will be judged by the logic pre-programmed in the questionnaire that you will see, if you agree to participate.

3. **Do I have to take part in this research study?**
Participation in any research project is voluntary. If you do not want to take part, you do not have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.
If you decide you want to take part in the research study, you will be asked to:
- Read the information carefully (ask questions if necessary);
- If you would like to participate, sign the consent form;.

4. **What does participation in this research require, and are there any risks involved?**
If you are eligible and decide to take part in the research study, you will be randomly assigned to either **Group A** (receive monthly reminders to remind you to test for HIV/STIs) or **Group B** (no monthly reminders). We will ask you to complete the following tasks:

[Completion of Questionnaires]

Today, the research team will ask you to complete an iPad-based questionnaire. This questionnaire will ask you questions about your socio-demographic characteristics, sexual behaviours, HIV/STI testing and diagnosis experiences, attitudes towards HIV pre-exposure prophylaxis, blood donation experiences, and geo-social networking app use experiences. It should take approximately 15 minutes to complete.
At 6 months, the research team will ask you to complete another online questionnaire. This questionnaire will ask you questions about your experiences in the past 6 months, including sexual behaviours, HIV/STI testing and diagnosis experiences, blood donation experiences, and geo-social networking app use experiences. It should take approximately 10 minutes to complete.

At 12 months, the research team will ask you to come back to this site to complete another iPad-based questionnaire. This questionnaire will ask you questions about your experiences in the past 6 months, including sexual behaviours, HIV/STI testing and diagnosis experiences, blood donation experiences, and geo-social networking app use experiences. It should take approximately 10 minutes to complete.

If you are assigned to **Group A**, at 6 and 12 months you will also be asked questions about your experience of the monthly reminders including the impact of the intervention on

your everyday life, mental health, sexual health and general health. You will not be asked these questions if you are assigned to **Group B**.

We don't expect these questionnaires to cause any harm or discomfort, however if you experience feelings of distress as a result of participation in this study you can let the research team know and they will provide you with assistance. Alternatively lists of services are provided in the contact details below to assist you if necessary.

[Collection of biospecimen]
Today, a study nurse will collect the following biospecimen from you: an anal swab, a urine sample and 10ml of blood sample. A doctor will also check ano-genital warts for you. It should take approximately 20 minutes to complete.

At 12 months, in the last survey, the research team will ask you to come back to this site. Besides a questionnaire, a study nurse will collect the following biospecimen from you: an anal swab, a urine sample and 10ml of blood sample. A doctor will also check ano-genital warts for you. It should take approximately 20 minutes to complete.

[HIV/STI testing]
Today and at 12 months when you come to this site for the last onsite survey, you will be tested for HIV, syphilis, urethral and anal chlamydia and gonorrohea, and examined for anogenital warts. CD4+ testing will be provided for you if you are diagnosed with HIV. HIV/STIs will be treated as per relevant treatment guidelines in China.

[SMS reminders]
We acknowledge that directly mentioning of sensitive words such as HIV and STIs in SMS reminders may lead to the exposure of privacy of participants to others. As a result, we will avoid using these sensitive words in actual SMS reminders. Instead, in actual reminders we will use "**Little A**" to refer to "HIV", "**Little B**" to refer to "STIs", "**Health check-up**" to refer to "HIV/STI testing", "**Self check-up**" to refer to "HIV self-testing at home" and "health kit" to refer to "condoms/lubes/health manuals".

If you are in **Group A**, after completion of the iPad-based questionnaire you will receive ***Message A***: "A gentle reminder: If you plan to have a health check again in the next 12 months, welcome to our center. If you do it elsewhere (including self-health check) in the next 12 months, please register the results online at the following link: ******. Every time you register we will compensate you with an electronic mobile phone credit of CNY10 (USD1.5). If you change your mobile phone number in the next 12 months please let us know." Tomorrow, you will receive ***Message B***: "A gentle reminder: ***Little A*** and ***Little B*** are spreading rapidly and it's hard to detect by yourself. Your best protection is a regular check-up (e.g. every 3 months). If you change your mobile phone number please let us know." Starting from day 30, you will receive ***Message C*** every 30 days: "A gentle reminder: If you have not had a health check in the past 3 months please do so as soon as possible. If you change your mobile phone number please let us know." On day 190, you will receive ***Message D***: "A gentle reminder: please complete a survey at the following link at your earliest convenience: ******. We will compensate you with an electronic mobile phone credit of CNY50 (USD8). If you change your mobile phone number please let us know." On day 370, you will receive ***Message E***, reminding you to complete an onsite survey about your sexual life and testing behaviours in the past 6 months: "A gentle reminder: please attend our center to complete the final survey. We will compensate you with an electronic mobile phone credit of CNY100 (USD16), together with a health kit. If you change your mobile phone number please let us know."

If you assigned to **Group B,** you will receive ***Message A*** today, ***Message D*** on day 190 and ***Message E*** on 370. You will not receive ***Messages B*** and ***C***.

You are free to withdraw from the SMS reminders by calling our study phone number at any time. You are free to withdraw from the research at any time. If you withdraw from the research we will destroy any information that has already been collected.

5. What are the possible benefits to participation?

We hope to use information we get from this research study to benefit other men who have sex with men who are at high risk for HIV/STI infection but do not test frequently enough to get diagnosed on a timely basis. You will benefit from this study with free and professional HIV/STI counselling and testing services, referral and treatment services if applicable. You will also get free condoms, lubricant and health manual.

6. What will happen to information about me?

By signing the consent form you consent to the research team collecting and using information about you for the research study, if you are eligible and willing to participate in this study. If you provide your permission the research team will store your data in a password-protected databank for 5 years. The data will be stored in a format where you will be identifiable. This is designed to match your data with you in follow-up visits in this study. However, only the custodians listed in the table above will have access to your original data. All identifying variables, including the initial of your surname, mobile phone number and date of birth, will be de-identified before data are transferred to a data analyst in this study. The custodians listed in the table above will ensure that your data is stored and managed appropriately and according to the relevant privacy laws. The data custodian will only share your data with researchers who are conducting HIV/STI related epidemiologic studies and only once these projects have received separate ethics approval from a Human Research Ethics Committee. All identifying variables, including initial of your surname, mobile phone number and date of birth, will be de-identified before data sharing.

7. How and when will I find out what the results of the research study are?

The research team intend to publish and report the results of the research study in a variety of ways, including academic conferences and journals. All information published will be done in a way that will not identify you. If you would like to receive a copy of the results you can let the research team know by adding your email within the consent form. We will only use these details to send you the results of the research. The results will also be made available via the school's website: kirby.unsw.edu.au.

8. What if I want to withdraw from the research study?

If you do consent to participate, you may withdraw at any time. You can do so by completing the 'Withdrawal of Consent Form' which is provided at the end of this document. Alternatively you can ring the research team and tell them you no longer want to participate. If you decide to leave the research study, the researchers will not collect additional information from you. Your decision not to participate will not affect your relationship with the Guangdong Provincial Center for Skin Disease and STI Control, the Wuxi Municipal Center for Disease Control and Prevention, the Nanshan District Center for Chronic Disease Control and Prevention, the Kirby Institute, University of New South Wales, and the Sun Yat-sen University, Guangzhou

9. What type of data will be stored in this data bank?

With your permission we would like to store the following types of data with the intention to share it and use it in future research projects.

- Socio-demographic characteristics, including your name (a pseudonym is ok), initial of your surname, mobile phone number, date of birth, ethnicity, marital status, educational level, income and profession.
- Sexual behaviours, including anal sex with men and vaginal sex with women and condom use during these sex.
- HIV/STI testing and diagnosis experiences
- Attitudes towards HIV pre-exposure prophylaxis
- Blood donation experiences
- Geo-social networking app use experiences
- Bio-specimen to test for HIV and other STIs

10. What will happen to my data?

If you provide your permission the research team will store your data in a

password-protected databank. The data stored in a format where you will be identifiable. This is designed to match your data with you in follow-up visits in this study. However, only the custodians listed in the table above will have access to your original data. All identifying variables, including name (a pseudonym is ok), initial of your surname, mobile phone number and date of birth, will be de-identified before data are transferred to a data analyst in this study.

11. Who will have access to my data?

Only the custodians listed in below will ensure that your data is stored and managed appropriately and according to the relevant privacy laws. The data custodian will only share your data with researchers who are conducting HIV/STI testing related epidemiologic studies and only once these projects have received separate ethics approval from a Human Research Ethics Committee. All identifying variables, including name (a pseudonym is ok), initial of your surname, mobile phone number and date of birth, will be de-identified before data sharing.

Data Custodians	*Mr. Yunyun Zhu*	*Guangdong Provincial Center for Skin Disease and STI Control, China*

12. How long will you store my data for?

We intend to store your data for 5 years. After 5 years, the data from the questionnaire will be deleted from the computer system and biospecimen will be disposed of as per biosafety practice in China.

13. Can I withdraw my information from this databank?

If you no longer wish to have your data stored or do not wish to be contacted for research purposes you can withdraw your information by completing the withdrawal of consent form that is attached or by phoning the data custodian and letting them know.

14. What should I do if I have further questions about my involvement in the research study?

The person you may need to contact will depend on the nature of your query. If you want any further information concerning this project or if you have any problems which may be related to your involvement in the project, you can contact the following member/s of the research team.

15. Research Team Contact Details

Name	*Dr. Huachun Zou*
Position	*Research Fellow*
Telephone	*+61 2 9385 3132 or +86 20 8733 5651*
Email	*hzou@kirby.unsw.edu.au*

16. Support Services Contact Details

We don't expect this study procedure to cause any distress, however if you experience feelings of distress as a result of participation in this study you can let the research team know and they will provide you with assistance. If at any stage during the project you become distressed or require additional support from someone not involved in the research please call:

Name/Organisation	*Dr. Weiying Chen/T2T Project*
Position	*Research Assistant*
Telephone	*189 2249 3020*
Email	T2TStudy@outlook.com

What if I have a complaint or any concerns about the research study?

If you have any complaints about any aspect of the project, the way it is being conducted, then you may contact:

Complaints Contact

Position	Human Research Ethics Coordinator
Telephone	+ 61 2 9385 6222
Email	humanethics@unsw.edu.au
HC Reference Number	HC16803

BMJ Open

A randomized controlled trial to evaluate the impact of sexual-health-clinic-based automated text message reminders on the testing of HIV and other sexually transmitted infections in men who have sex with men in China: protocol for the T2T Study

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Keywords:	Text message service, Reminder, HIV, STI, Men who have sex with men, Sexual health clinic

A randomized controlled trial to evaluate the impact of sexual-health-clinic-based automated text message reminders on the testing of HIV and other sexually transmitted infections in men who have sex with men in China: protocol for the T2T Study

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ABSTRACT

Introduction: The frequency of screening for HIV and other sexually transmitted infections (STIs) among men who have sex with men (MSM) is still low in China.

Methods and analysis: A sexual health clinic (SHC)-based randomized controlled trial will be conducted in Guangzhou, Wuxi and Shenzhen, China, enrolling 600 MSM. Eligibility will be judged by the pre-programed iPad-based questionnaire: 1) be >=18 years of age, and 2) have had 2 or more male anal sex partners, or condomless anal sex with a casual male sex partner, or an STI history, in the past 6 months, and 3) provide a valid mobile number. Eligible men will be randomly allocated 1:1 to either Intervention Arm (with monthly text message reminding them to test for HIV/STIs) or Control Arm (without reminder). Men in both arms will complete a questionnaire onsite at enrollment and 12 months, and another questionnaire online at 6 months. Men in both arms will be tested for HIV, syphilis, anal gonorrhea/chlamydia, and penile gonorrhea/chlamydia at enrollment and 12 months. The primary outcome is the rate and frequency of HIV testing within the 12 months after enrolment. The secondary outcome is the rate of unprotected anal intercourse. An assessment of the cost-effectiveness of this intervention is also planned.

Ethics and dissemination: The study has been approved by the Ethical Review Committees of the University of New South Wales in Australia (HC16803), the Guangdong Provincial Center for Skin Disease and STI Control (GDDHLS-20160926) and Wuxi Center for Disease Control and Prevention (WXCDC2016009) in China. Study findings will be submitted to academic journals and disseminated to local health authorities.

Trial registration number: This study has been registered at the Chinese Clinical Trial Registry (http://www.chictr.org.cn/enIndex.aspx) and WHO International Clinical Trials Registry Platform (http://www.who.int/ictrp/en/), ID: ChiCTR-IPR-15006086.

Keywords

Text message service; Reminder; HIV; STI; Men who have sex with men; Sexual

health clinic

ARTICLE SUMMARY

Strengths and limitations of this study

- No study has examined the role of sexual health clinic based automated short messaging services in the testing and detection of HIV/STIs in men who have sex with men (MSM) in China.
- Findings from this study has the potential to help health authorities to develop new interventional strategies to control HIV/STIs among MSM in China.
- This intervention, from judging eligibility to sending text message reminders, is wholly automated and requires limited human input, which can be easily replicated in other sexual health clinics in China and beyond.
- Sexual behaviours and STI history during follow-up will be self-reported by participants, which may be subject to bias.
- Loss to follow-up of participants is possible in this longitudinal study.

INTRODUCTION

Men who have sex with men (MSM) in many countries are disproportionately affected by HIV and other sexually transmissible infections (STIs) such as gonorrhoea, chlamydia and syphilis[1-4]. More frequent screening for HIV and other STIs has the potential to improve detection of these largely asymptomatic infections, interrupting transmission and improving disease control [5]. Guidelines in a number of countries call for regular screening for HIV/STIs among MSM. For example, the US and Australian guidelines recommend that all MSM be screened for urethral and rectal chlamydia, pharyngeal and rectal gonorrhea, syphilis and HIV at least once a year, with 3-6 monthly screening of MSM at higher-risk for HIV/STIs transmission [6 7]. However, available data suggest that the rate of screening for these infections among MSM is much lower than recommended in many countries[8 9].

Significant increases in screening rates for gonorrhoea and chlamydia (Odds ratio (OR) range:1.4-1.9) have been demonstrated in observational studies using several different strategies: use of a computer alert on an electronic medical record [10], the introduction of clinic guidelines on STI screening [11], and short text messaging reminders for repeat STI screening [12 13]. Increases in syphilis testing (OR range: 2.3-21.4) were found using the following strategies: advocating regular serological screening for syphilis during routine HIV care [14]; including syphilis serology testing routinely with blood tests performed as part of HIV monitoring [15]; use of a computer alert on an electronic medical record [16]; and an electronic medical record system with a reminder to clinicians to enhance syphilis retesting following syphilis treatment [17]. A

before-and-after study in Australia using existing clinical and behavioral data of clients attending a major sexual health clinic (SHC) found that automated, computer-generated text message service (SMS) 3-monthly reminders doubled the testing rate for HIV, syphilis, gonorrhoea and chlamydia among MSM [18]. That study also demonstrated an increased detection rate for syphilis, gonorrhoea and chlamydia, but not for HIV [18]. Another before-and-after study in Australia found increased HIV/STI re-testing rates among MSM as a result of 3-6 monthly SMS reminders at a large SHC [12]. However until now there has been no randomized controlled trial to confirm these effects.

MSM in China are increasingly engaging in high risk sexual behaviors such as low rate of condom use in anal sex, multiple concurrent partnerships and drug use during sex [19]. The rates of HIV and STIs among this population are high and increasing. The estimated HIV prevalence among MSM in China increased sharply over the past decade: from 0.6% in 2003 to 8% in 2015 [20 21]. Accordingly the proportion of MSM among all people living with HIV/AIDS also climbed steadily: from 7% in 2005 to 25% in 2015 [22 23]. Many MSM in China were also infected with other STIs. A meta-analysis found that the prevalence levels of STIs among MSM in China were 6% for chlamydia, 2% for genital warts, 2% for gonorrhoea, 9% for hepatitis B, 1% for hepatitis C, 66% for human papillomavirus and 11% for herpes simplex virus-2 [24]. However the testing rate for these infections was suboptimal. A systematic review found that less than 40% of MSM in China had tested for HIV in the past year [25]. Nearly half of MSM in China had a baseline CD4+ Cell count <= 350 per mm^3 at

HIV diagnosis [26]. The rates of testing for other STIs were also low [27 28]. It is urgently needed to introduce an effective intervention that can increase testing and help achieve timely diagnosis of HIV and other STIs among MSM in China.

Our study aims to use a randomized controlled trial to evaluate the role of SHC-based automated text message services in the testing and detection of HIV and other STIs among MSM in China.

METHODS AND ANALYSIS

Overview

The proposed protocol (dated December 8, 2016) was developed and facilitated by collaborations between experienced investigators from the Kirby Institute, the University of New South Wales (UNSW) in Sydney, Australia, Dermatology Hospital of Southern Medical University (DHSMU) in Guangzhou, China, Wuxi Center for Disease Control and Prevention (CDC) in Wuxi, China, Nanshan District Center for Chronic Disease Control and Prevention (CCDC) in Shenzhen, China, and Sun Yat-sen University in Guangzhou, China. The study will randomize 600 men who have sex with men (MSM) 1:1 into Intervention Group (with reminders) and Control Group (without reminders) and evaluate the role of SHC-based automated text message services in the testing and detection of HIV/STIs among MSM. A sample size of 300 MSM in each group will provide 90% power to detect a 15.0% (from 50% to 65%) difference in the proportion of HIV testing in the past 12 months between the two groups, considering 30% of loss-to-follow-up at 12 months.

Objectives

The primary objective of this study is to determine the impact of SHC-based automated text message services on the testing and detection of HIV. The secondary objective is to determine the impact of SHC-based automated text message services on the change in sexual behaviors. The additional analysis is to evaluate the costs and incremental cost-effectiveness of the intervention.

Study settings

This study will be based at the SHCs affiliated to DHSMU, Wuxi CDC and Shenzhen Nanshan CCDC. The population in Guangzhou, Wuxi and Shenzhen was around 13, 6 and 13 million, respectively, all with per capita gross domestic product (GDP) of over USD20,000 in 2014 [29-31]. The three SHCs provide HIV/syphilis voluntary counseling and testing (VCT) and HIV/STI treatment services to over 25,000 clients annually, 10% of whom were estimated to be MSM (data not published). These three SHCs are equipped with microbiological diagnostic units and capable of timely testing and treating HIV and other STIs, including syphilis, gonorrhea, chlamydia trachomatis and genital warts.

Inclusion criteria

MSM attending the three clinics will be invited to join the study if they meet the following criteria: 1) anatomical men aged 18 years or older; 2) having over 2 male

anal sex partners, or condomless anal sex with a casual male sex partner, or an STI history including gonorrhea, syphilis, anogenital warts, genital herpes and chlamydia trachomatis, in the past 6 months; 3) possessing a mobile phone; 4) willing to provide informed consent for the collection of demographics, sexual behaviors and HIV/STI testing experiences and biological samples to test for HIV/STIs; 5) residing in a study city in the next 12 months or visiting a study city frequently enough to participate in the study; 6) willing to register testing results if they test elsewhere during the study.

Exclusion criteria

MSM who meets one or more criteria listed below will be excluded: 1) has severe psychiatric illnesses; 2) unable to read or use the iPad questionnaire; 3) does not speak or read the Chinese languages

Study procedures

We will use the following strategies for achieving adequate participant enrolment to reach target sample size: 1) At the three clinics, study posters will be put in the waiting area, consultation rooms and male toilets. 2) The clinics will work with local MSM community organisations to refer potentially eligible MSM, who will physically attend the three clinics to complete the enrolment. 3) Doctors will encourage participants to introduce our study to their peers. A study phone number will be designated to this study. This randomized controlled trial will consist of computer-assisted self-interview (CASI) and automated, computer-generated SMS

reminders among 600 MSM attending the SHCs. It will be conducted over 21-24 months: 3 months of logistic preparation, 3-6 months of recruitment, 12 months of follow up and 3 months of report preparation. Detailed recruitment procedure is described in Figure 1 and Table 1. Over a 3-6 months recruiting period, all male clients presenting to the clinic will be given an information flyer by a receptionist who is not directly involved in the study. The flyer will include basic information about the study, including that it is a study for MSM. The receptionist will ask each male client to read the flyer and to visit the study research assistant who sits at a nearby desk, if they are interested in finding out more about the study. Clients may be enrolled and passed on to the research assistant when they are seen by a clinician after leaving the waiting area. Those male clients who express interest in participating will see the study research assistant, who will take them to a private clinic room where an iPad questionnaire system is installed. The study research assistant will explain what the study involves and go through the iPad-based full Participant Information and Consent Form (PICF) with potential eligible participants. Men will have time to read the PICF, to ask questions, and to decide if they will participate in the study. Men will need to click the "Agree" button to consent before completing an iPad-based questionnaire. The study research assistant will ask consented participants to complete the iPad-based questionnaire on their own, in the private room. They will be instructed that if they have any further questions, they should ask the research assistant who will be at a desk, outside of the private room. The questionnaire will collect information on sexual behaviours, HIV/STI testing behaviours and diagnosis

history and alcohol/tobacco/drug use. The pre-programmed logic in the questionnaire will judge if a participant is actually eligible, based on sexual behavior variables. Those who are not eligible will be thanked and released back into the clinic waiting room for their routine clinical care. Eligible participants will provide a valid mobile phone number and then be automatically randomised into either intervention or control group, by the computer. They will then receive a text message with a code as their Study ID. When they finish the PICF and questionnaire participants will see the study research assistant who will guide them to see a doctor for bio-specimen collection, followed by routine clinical care, if necessary. Eligible MSM who opt out of the study will be recorded and asked about reasons to decline. During the whole study period, the clients, clinicians, research assistants, and data analysts will be blinded after assignment to intervention. To maintain the overall quality and legitimacy of the trial, unblinding should occur only in exceptional circumstances when knowledge of the intervention can substantially increase HIV/STI retesting rate among MSM. We will judge this on the basis of the interim data analysis. If unblinding is deemed to be necessary, the steering committee of the study will hold a discuss and make a decision in consultation with the ethics committees.

Detailed study procedure is described in Figure 2. We acknowledge that directly mentioning of sensitive words such as HIV and STIs in SMS reminders may lead to the exposure of privacy of participants to others. As a result, we will avoid using these sensitive words in actual SMS reminders. Instead, in actual reminders we will use "*Little A*" to refer to "HIV", "*Little B*" to refer to "STIs", "*Health check*" to refer to

"HIV/STI testing", "*Self health check*" to refer to "HIV self-testing at home", and "health kit" to refer to "condoms/lubes/MSM health manuals". We will clarify this in the PICF. All messages will include a withdrawal option.

For MSM in the Intervention Group, upon enrolment, they will receive Message A: "A gentle reminder: If you plan to have a health check again in the next 12 months, welcome to our center. If you do it elsewhere (including self-health check) in the next 12 months, please register the results online at the following link: ******. Every time you register we will compensate you with an electronic mobile phone credit of CNY10 (USD1.5). If you change your mobile phone number in the next 12 months please let us know." When they register online, participants need to enter the mobile phone number that was validated at enrolment and the initial of their surname to enter the questionnaire. This is designed to avoid the exposure of sensitive questions to a non participant. On the second day after enrolment, they will receive Message B: "A gentle reminder: Little A and little B are spreading rapidly and it's hard to detect by yourself. Your best protection is a regular check-up (e.g. every 3 months). If you change your mobile phone number please let us know." Starting from day 30, they will receive Message C every 30 days: "A gentle reminder: If you have not had a health check in the past 3 months please do so as soon as possible. If you change your mobile phone number please let us know." On day 190, 10 days after they receive Message C on day 180, they will receive Message D, reminding them to complete an online survey about their sexual life and testing behaviors in the past 6 months: "A gentle reminder: please complete a survey at the following link at your earliest

convenience: ******. We will compensate you with an electronic mobile phone credit of CNY50 (USD8). If you change your mobile phone number please let us know." On day 370, 10 days after they receive Message C on day 360, they will receive Message E, reminding them to complete an onsite survey about their sexual life and testing behaviours in the past 6 months: "A gentle reminder: please attend our center to complete the final survey. We will compensate you with an electronic mobile phone credit of CNY100 (USD16), together with a health kit. If you change your mobile phone number please let us know." At enrollment and 12 months men will be tested for HIV, syphilis, urethral and anal chlamydia and gonorrohea, and examined for anogenital warts. CD4+ testing will be provided for men diagnosed with HIV. HIV/STIs will be treated as per relevant treatment guidelines in China. At 6 and 12 months men will also be asked questions about their experience of the intervention including the impact of the intervention on their everyday life, mental health, sexual health and general health (Figure 2).

MSM in the Control Group will receive Message A upon enrolment, Message D on day 190 and Message E on 370. They will not receive Messages B and C. They will complete the same questionnaire as men in the intervention group do at enrolment, 6 months and 12 months and test for above-mentioned HIV/STIs at enrolment and 12 months. They will not be asked about their experience of the intervention.

The 10 days' time gap between Messages C and D is planned to give men in both groups enough time to attend a SHC upon receiving Message C. Besides men's mobile phone number (compulsory) we will also try to collect other contact

information (optional), including email, QQ and WeChat ID (instant online messaging applications frequently used in China). At 6 and 12 months, men will be contacted with the additional contact information if they do not complete a designated survey within 7 days after Messages D and E are sent. Men who register testing information online or fill in an online questionnaire at 6 months will need to enter their mobile number to access the actual questionnaire. This is designed in case another person oversees the URL address from Message A. The process from commencing CASI to the regular dispatch of the reminders will be entirely automated, requiring no human input.

For men in both groups, at enrolment and 12 months, a study nurse will collect a swab from the anal canal to test for anal gonorrhea and chlamydia, and 5 ml of blood to test to test for HIV and syphilis. Participants will self-collect a urine sample to test for urethral gonorrhea and chlamydia. A doctor will check ano-genital warts for each participant. The HIV serologic status will be screened by ARCHITECT HIV Ag/Ab Combo assay (Abbott Laboratories, Abbott Park, Illinois, USA). Positive samples will be further screened by enzyme linked immunosorbent assay (ELISA) (Bio-Rad Laboratories, CA, USA). Samples positive for ELISA will be confirmed by the HIV-1/2 Western blot assay (HIV Blot 2.2 WB; Genelabs Diagnostics, Singapore). Confirmed HIV cases will be tested for CD4+ T Cell count. Syphilis will be screened by the toluidine red unheated serum test (TRUST) (RSbio, Shanghai, China) and samples positive for TRUST will be confirmed by treponema pallidum particle assay (TPPA) (Fuji ReBio, Tokyo, Japan). Anal and urethral gonorrhea and chlamydia will

be tested using polymerase chain reaction (PCR) (Roche Diagnostics, Shanghai, China). Ano-gential warts will be checked by a doctor with the assistance of acetic acid test.

Incentives and retention

Study participants will receive health education materials, condoms and lubricant upon completion of the CASI questionnaire at enrolment and 12 months. Participants will receive an electronic mobile phone credit of CNY50 (USD8), CNY50 (USD8) and CNY100 (USD16), upon completion of the surveys at enrolment, 6 months and 12 months. Participants who test elsewhere will receive an additional electronic mobile phone credit CNY 10 (USD 1.5) each time they register testing results online.

Statistical methods

Power/sample size

We used the following formula to calculate sample size:

$$n = \frac{(Z_\alpha \sqrt{2\overline{pq}} + Z_\beta \sqrt{p_0 q_0 + p_1 q_1})^2}{(p_1 - p_0)^2}$$

In this formula, Z_α and Z_β represent the Z boundaries under the standard normal distribution; p_1 and p_0 represents proportion of a parameter in the intervention group and control group, respectively; p equals to the average of p_1 and p_0; q=1-p. We used 2 parameters in the calculation of sample size: (a) proportion of men who have HIV testing during the 12 months after baseline; (b) proportion of men who have condomless anal sex during the 12 months after baseline. We assumed a two-sided

hypothesis test with a 5% significance level ($Z_{\alpha/2}$=1.96), a desired power of 90% (Z_{β}=1.28), and that both groups will have the same number of observations.

Using parameter (a), the rate of HIV testing in the past 12 months among MSM in Wuxi in 2014 was 50% (p_0), and this figure was expected to increase to 65% (p_1) according to a before-and-after study in Australia [18]. This resulted in a sample size of 225 in each group. Khosropour et al., retained around 70% of MSM for 12 months using bimonthly follow-up surveys through text messages [30]. We will adopt a number of strategies to minimize the loss-to-follow-up rate: educating investigators about the culture in MSM community and develop rapport with participants; verifying mobile number at enrolment; contacting participants on days 190 and 370 using various messaging softwares/apps such as WeChat, QQ, email, etc; and reasonable incentives. Considering a loss-to-follow-up rate of 30%, a sample size of 300 MSM in each group will be needed.

Analysis plan

Analyses will be performed using STATA 13.0 (College Station, TX, USA) statistical analysis software. All effects will be estimated with a 95% confidence intervals and p-values from the corresponding hypothesis tests. Statistical significance will be taken as two-sided p-value less than 0.05, with no adjustment for multiple comparisons. Characteristics of groups will be summarised at baseline and across study arms. Mean duration of study follow-up will be compared by group.

Primary analysis will compare randomized groups of MSM using an intention to treat approach. Initial analyses will be simple, unadjusted comparisons of randomised groups. If there appears to be any important imbalances between randomised groups in terms of baseline covariates, adjusted analyses will also be performed.

The primary outcome is the proportion of HIV/STIs testing and detection during the past 12 months, comparing the intervention and control arms. At the end of the study: 1) we will use Cox proportional hazard models with Kaplan Meier plots and log-rank test to explore the cumulative rate of reported HIV/STIs testing and detection during the previous 12 months, comparing the two groups. Number of testing and detection of each infection will also be compared. 2) we will use Chi-square test to compare the proportion of reported HIV/STIs testing and detection during the previous 12 months before intervention with that during the 12 months after intervention, within Intervention Group. Number of testing and detection of each infection will also be compared.

The second outcome is the proportion of condomless anal sex during the past 12 months. At the end of the study: 1) we will use Chi-square test to compare the proportion of reported condomless anal sex during the previous 12 months between the two groups. 2) we will use rank sum test to compare the number of reported anal sex partners during the previous 12 months between the two groups. 3) we will use Chi-square test to compare the proportion of reported condomless anal sex during the previous 12 months before intervention with that during the 12 months after

intervention, within Intervention Group. 4) we will use rank sum test to compare the number of reported anal sex partners during the previous 12 months before intervention with that during the 12 months after intervention, within Intervention Group.

Additional analyses

Cost and cost-effectiveness evaluation

Although some studies have assessed the cost-effectiveness of HIV testing methods among high-risk populations in some regions [32-38], whether the intervention in this study is cost-effective is unclear. As a result, the costs and incremental cost-effectiveness of the intervention compared to control will be evaluated, using standard methods of cost-effectiveness analysis [39]. Our analysis will include the costs of the self-registration and SMS reminding system development and maintenance, HIV/STI testing and counseling, follow-up, and treatment. All costs will be measured from a societal perspective, and inflated to 2015 Chinese Yuan at a discounting rate of 3% annually.

Cost-Effectiveness analysis

Based on incremental cost-effectiveness analysis, we will calculate the incremental cost for one additional newly identified HIV/STI case, and one additional early HIV case, using the following formula [39]:

ICERij = (Ci—Cj) / （Ei - Ej）

Markov model based Cost-Utility analysis

We will develop a decision model to reflect when successful HIV/STI detection, follow-up, and treatment occur for a cohort of MSM with/without intervention, and then a Markov model estimating the lifecycle of MSM from entering the cohort until death, to examine the incremental cost-utility of intervention. Effectiveness is measured as quality adjusted life-years (QALYs) gained. We assume that QALYs accrues by early initiation of antiretroviral therapy (ART) following early HIV detection. According to the actual situation in China, the natural history of HIV/AIDS is categorized as the following stages: asymptomatic HIV, symptomatic HIV, AIDS and death Health states summarizes current status based on CD4+ T cell count, quality of life, ART usage and resource use. ART and CD4+ T cell count combined determines the transition probabilities and mortality rates [40 41]. The model will assess HIV status, stage transfer and its consequences among MSM with incident HIV infection on an annual basis. All the parameters used in this model will be compiled from a variety of sources, including literature review, ongoing cohort studies and investigations, surveillance data or unpublished data from Wuxi and other parts of China.

In this study, we assume that: (1) stage transition in the Markov model happens once a year, (2) once an HIV infected man receives ART, he will complete the entire treatment procedure. To account for assumptions and uncertainties of this model, we will perform one-way sensitivity analyses on all model parameters. For all the

probability variables, our ranges for sensitivity analyses represent our judgment of the variation on the basis of both the literature and discussion with experts.

Sample/data storage

All electronic questionnaires, consent forms will be stored in a password-protected computer at the information center at DHSMU as per its common practice. The data will be stored in a format that is identifiable. This is designed to match data with individual participants in follow-up visits in this study. However, only the custodian will have access to the original data. All identifying variables, including name (a pseudonym is ok), initial of participant's surname, mobile phone number and date of birth, will be de-identified before data are transferred to a data analyst in this study. The custodian will ensure that data is stored and managed appropriately and according to the relevant privacy laws. The data custodian will only share data with researchers who are conducting HIV/STI testing related epidemiologic studies and only once these projects have received separate ethics approval from a Human Research Ethics Committee. All identifying variables, including name (a pseudonym is ok), initial of participant's surname, mobile phone number and date of birth, will be de-identified before data sharing. Bio-specimen collected at a given site will be stored at the corresponding participatory institution.

ETHICS AND DISSEMINATION

The study has been approved by the Ethical Review Committees of the University of

New South Wales in Australia (HC16803), the Dermatology Hospital of Southern Medical University (GDDHLS-20160926) and Wuxi Center for Disease Control and Prevention (WXCDC2016009) in China. We anticipate that the benefits of study participation will outweigh any risks, including loss of confidentiality and privacy of clinical information. Participants will benefit from frequent testing and early diagnosis of HIV/STIs and timely treatment if positive. The findings of the study will be disseminated to local and national government in China as well as the wider academic audience and public health organizations through peer-reviewed publications and international conferences.

DISCUSSION

This study protocol describes a randomized controlled trial designed to increase the testing and detection of HIV and other STIs among Chinese MSM through computer-assisted self-interview and automated computer generated reminders. Firstly, we seek to develop a platform requiring limited investment and human power that could be easily replicated and deployed in other SHCs in China and beyond. As such, one of the challenges in designing the intervention was the acceptance of it among target population-MSM in China-a population that has long been marginalized and discriminated against. Fortunately in our unpublished pre-trial study, almost 80% of MSM in the community were willing to take such an intervention. It is estimated that this rate would be even higher among MSM attending SHCs. Other key challenges to this study include the need to sustain the

motivation of clinic staff to participate in the study while addressing the multiple competing health priorities. Secondly, we will be able to understand MSM with what characteristics are more likely to take this intervention and barriers that prevent other MSM from taking this intervention. This will help develop an intervention that is contextualized and tailored to the characteristics of MSM. Thirdly, if successful, this intervention with high potential cost-effectiveness will contribute to the compilation of the fabric of quality SHCs and health providers that will eventually be readily available to MSM at their finger tips. This will greatly encourage and facilitate them to test for HIV/STIs on a more frequent basis. Lastly, results from this study may facilitate the development of proactive interventions strategies targeting other at-risk populations, such as female sex workers and their clients, and drug users, etc. to increase the testing and detection of HIV and other STIs and hence prevent the transmission of these infections.

This intervention has its limitations: Firstly, the 12-months research period is a long commitment for MSM as many of them are quite mobile. The retention rate could be compromised by 12 months. To tackle this problem we will verify participants' mobile phone number at enrolment and remind them to update their mobile number every 30 days. Additionally we will also use other contact information reported by participants to achieve the highest possible retention rate. Secondly, men could forget to register testing experience from other venues. To tackle this problem, we will remind them to do this in Message A at enrolment. Because a similar reminder during the study would potentially bring about

contamination to the intervention, we will not send further reminders. Thirdly, as this intervention will be conducted in metropolitan cities, the results may not apply to that in other settings.

In summary the knowledge gained from this study may be used to design similar protocols with a higher number of participants and appropriate intervention strategies to reduce the burden of HIV and other STIs among MSM, a population who is heavily burdened by these infections. Additionally, if the results are positive, we will scale up this practice in more SHCs across China.

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Authors' contribution

Huachun Zou and Xiaojun Meng initiated this research plan and designed this protocol with Bin Yang and Andrew Grulich consulting on ethics and feasibility of the research. Zhenzhou Luo, Tianjian Jia, Xuan Zhang, Yi Ding and Ligang Yang provided expertise on recruitment and sample collection and will supervise these aspects at the three study clinics. Jinmei Huang, Shujie Huang and Heping Zheng provided expertise on sample testing and storage. Weiying Chen helped with the design of questionnaire and recruitment methods.

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Research Commission (NHMRC) Early Career Fellowship (APP1092621) and research grants from Guangdong Provincial Center for Skin Disease and STI Control (YCS201669), Wuxi municipal health and Family Planning Commission (MS201613), Wuxi Municipal Science and Technology Bureau (CSZ0N1512) and Nanshan District Center for Chronic Disease Control and Prevention. The funding bodies other than NHMRC participated in study design, data collection and analysis, preparation of the manuscript, and the decision to publish.

Competing interests

All authors declare no competing interests.

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Figure 1. Folow chart of recruitment

Figure 2. Folow chart of study procedure

Table 1. Schematic diagram of study procedure

Procedure	Timeline										
	D-180	D1	D2	D30*	D180	D190	D240	D300	D360	D370	D540
Logistics preparation	√										
Enrolment and allocation		√									
Message A sent to both arms		√									
Message B sent to intervention arm			√								
Message C sent to intervention arm				√	√				√		
Message D sent to both arms					√						
Message E sent to both arms									√		
M6 follow-up of both arms						√					
M12 follow-up of both arms										√	
Baseline data analysis							√				
Interim data analysis								√			
Follow-up data analysis											√

Notes:

D refers to day, D-180 means 180 days before enrolment.

* Beginning from day 30, Message C will be sent to intervention arm every 30 days until day 360.

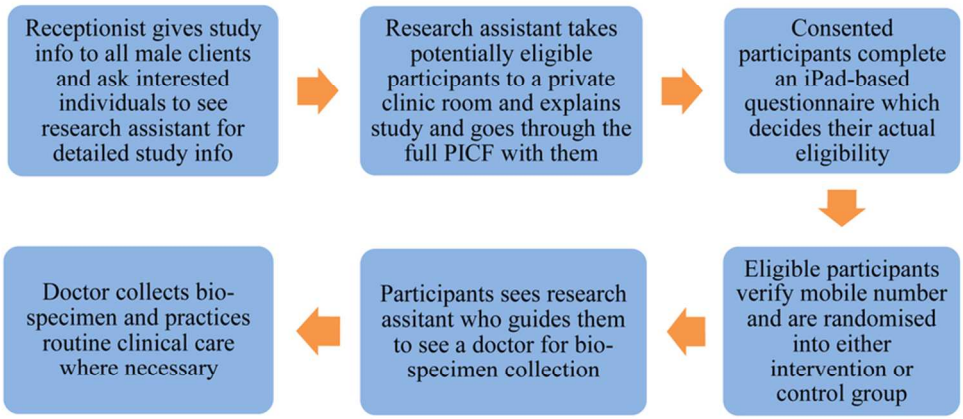

Figure 1. Flow chart of recruitment

Figure 1

83x40mm (300 x 300 DPI)

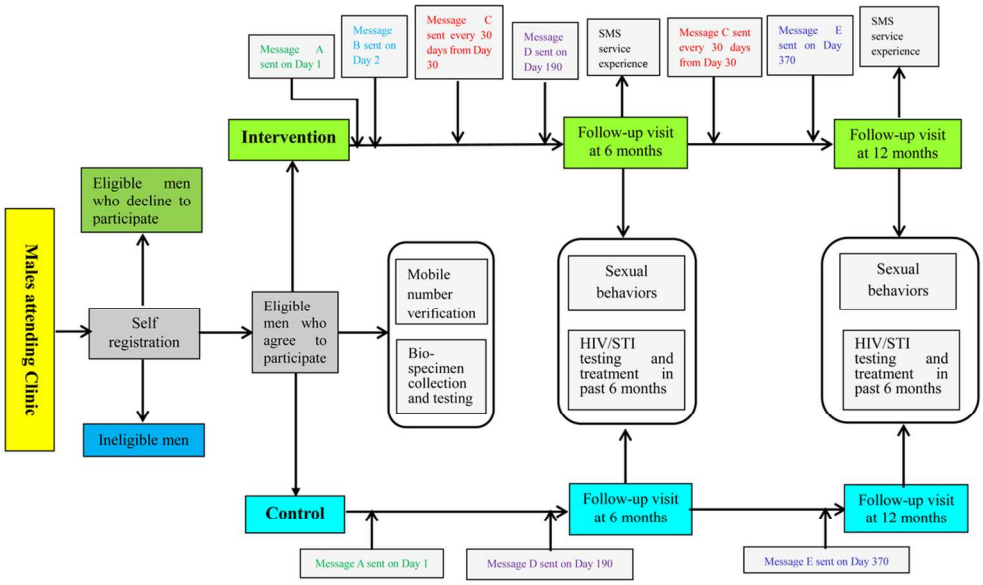

Figure 2. Flowchart of study procedure

Figure 2

109x68mm (300 x 300 DPI)

UNSW Human Research Ethics Application Form

More than Low Risk OR Low Risk Research Applications

Project Description Template

1. Lay Summary & Aims (Maximum of 500 words)
Briefly provide a summary of the project in lay terminology (no more than 500 words). The project summary should include the following details: • Aims of the project • Importance of the study
Our study aims to use a randomized controlled trial (RCT) to evaluate the role of sexual health clinic (SHC)-based automated short message service (SMS) reminders in the testing and detection of HIV and other sexually transmitted infections (STIs) among men who have sex with men (MSM) in China. At baseline, all male clients will be given an information flyer by a receptionist who is not directly involved in the study. The flyer includes the basic information about the study. Participants will then read the information, decide whether they might meet the inclusion criteria and decide whether they would like to participate. Potentially eligible participants who are willing and able to participate will be guided by the receptionist to a private clinic room where they will see the full Participant Information and Consent Form (PICF) for the study on an iPad. Consented participants will complete a questionnaire on the iPad. Eligibility will be judged by the pre-programmed logic in the questionnaire. After these steps, our research assistant will take eligible participants to see a doctor for biospecimen collection, followed by routine clinical care, in necessary. Eligible participants will be randomly allocated by the computer to either intervention group where they will receive monthly SMS reminders to test for HIV/STIs, or control group where they will not receive such reminders. At 6 and 12 months, participants in both groups will complete an online questionnaire and an onsite questionnaire, respectively, about sexual behaviours, HIV/STI testing behaviours and diagnosis history and alcohol/tobacco/drug use in the past 6 months. Participants in the intervention groups will also be asked about their experiences of SMS reminders in the past 6 months. At baseline and 12 months, an anal swab sample, a urine sample and a blood sample will be collected to test for gonorrhoea, chlamydia, syphilis and HIV. Anogenital warts will also be checked by a clinician. The primary outcome is the rate of HIV/STI testing in the past 12 months will be compared between the two groups. Secondary outcomes include the impact of intervention on sexual health behaviours and cost-effectiveness of intervention. This study is the first to examine the role of SHC-based automated SMS reminders in the testing and detection of HIV/STIs in MSM in China. Findings from this study has the potential to help health authorities to develop new interventional strategies to control HIV/STIs among MSM in China. The intervention, from identifying target population to sending text message reminders, is wholly automated and requires limited human input, which can potentially be easily replicated in other SHCs in China and beyond.
2. Background Literature Review – (Maximum of 500 words)
Provide an outline of the theoretical background for the research proposal with reference to relevant literature. • The background literature review should be "based on a thorough study of the current literature, as well as previous studies" (NS 1.1c) along with; • The potential significance of the study
MSM in many countries are disproportionately affected by HIV and other STIs [1-4]. More frequent screening has the potential to improve detection of these largely asymptomatic infections, interrupting transmission and improving disease control [5]. Guidelines in a number of countries call for regular screening for HIV/STIs among MSM. For example, the US and Australian guidelines recommend that all MSM be screened for urethral and rectal chlamydia, pharyngeal and rectal gonorrhea, syphilis and HIV at least once a year, with 3-6 monthly screening of MSM at higher-risk for HIV/STIs transmission [6, 7]. However, available data suggest that the rate of screening for these infections among MSM is much lower than recommended in many countries [8, 9]. Significant increases in screening rates for gonorrhoea and chlamydia (Odds ratio (OR) range:1.4-1.9) have been demonstrated in observational studies using several different strategies: use of a computer

alert on an electronic medical record [10], the introduction of clinic guidelines on STI screening [11], and short text messaging reminders for repeat STI screening [12]. Increases in syphilis testing (OR range: 2.3-21.4) were found using the following strategies: advocating regular serological screening for syphilis during routine HIV care [13]; including syphilis serology testing routinely with blood tests performed as part of HIV monitoring [14]; use of a computer alert on an electronic medical record [15]; and an electronic medical record system with a reminder to clinicians to enhance syphilis retesting following syphilis treatment [16]. A before-and-after study in Australia using existing clinical and behavioral data of clients attending a major sexual health clinic (SHC) found that automated, computer-generated short message service (SMS) 3-monthly reminders doubled the testing rate for HIV, syphilis, gonorrhoea and chlamydia among MSM [17]. That study also demonstrated an increased detection rate for syphilis, gonorrhoea and chlamydia, but not for HIV [17]. Another before-and-after study in Australia found increased HIV/STI re-testing rates among MSM as a result of 3-6 monthly SMS reminders at a large SHC [12]. However until now there has been no randomized controlled trial to confirm these effects.

MSM in China are increasingly engaging in high risk sexual behaviors such as low rate of condom use in anal sex, multiple concurrent partnerships and drug use during sex [18]. The rates of HIV and STIs among this population are high and increasing. The estimated HIV prevalence among MSM in China increased sharply over the past decade: from 0.6% in 2003 to 8% in 2015 [19, 20]. Accordingly the proportion of MSM among all people living with HIV/AIDS also climbed steadily: from 7% in 2005 to 25% in 2015 [21, 22]. Many MSM in China were also infected with other STIs. A meta-analysis found that the prevalence levels of STIs among MSM in China were 6% for chlamydia, 2% for genital warts, 2% for gonorrhoea, 9% for hepatitis B, 1% for hepatitis C, 66% for human papillomavirus and 11% for herpes simplex virus-2 [23]. However the testing rate for these infections was suboptimal. A systematic review found that less than 40% of MSM in China had tested for HIV in the past year [24]. Nearly half of MSM in China had a baseline CD4+ Cell count <= 350 per mm3 at HIV diagnosis [25]. The rates of testing for other STIs were also low [26, 27]. It is urgently needed to introduce an effective intervention that can increase testing and help achieve timely diagnosis of HIV and other STIs among MSM in China.

Findings from this study has the potential to help health authorities to develop new interventional strategies to control HIV/STIs among MSM in China. This interventional model can potentially be easily replicated in other SHCs in China and beyond.

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3. Research Design and Methodology (Maximum 1 page)

Provide an outline of the research design, the study timeline and data collection methods.

This randomized controlled trial will consist of computer-assisted self-interview (CASI) and mobile-phone-based intervention of 600 MSM attending the SHCs affiliated to the Guangdong Provincial Center for Skin Disease and STI Control, the Wuxi Municipal Center for Disease Control and Prevention, and the Nanshan District Center for Chronic Disease Control and Prevention.

Study Timeline

The study will be conducted over 21-24 months: 3 months of logistic preparation, 3-6 months of recruitment, 12 months of follow up and 3 months of report preparation.

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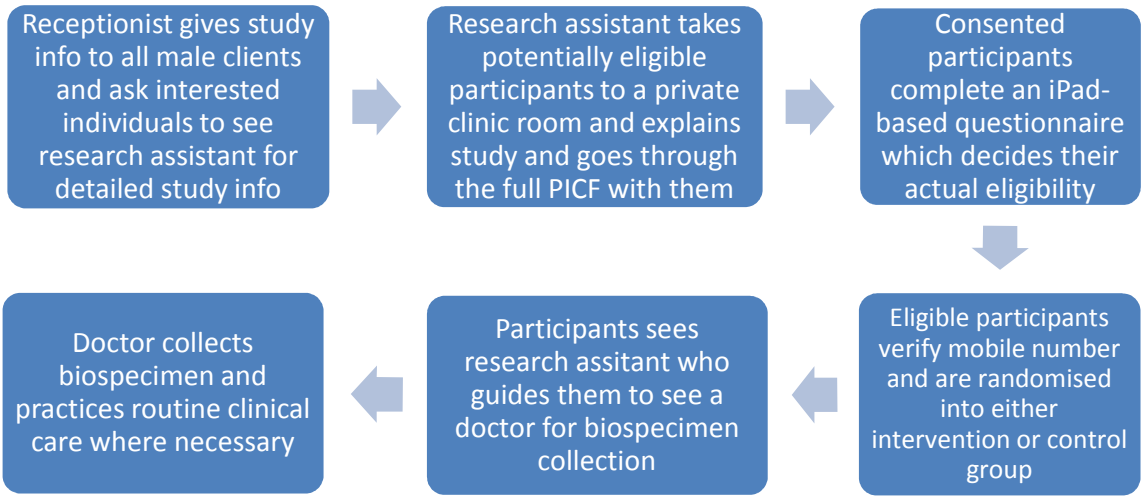
Study Methodology

Recruitment and screening:

The following is a step by step summary of the recruitment method (Fig 1):

1. All male clients presenting to the clinic will be given an information flyer by a receptionist who is not directly involved in the study. The flyer will include basic information about the study, including that it is a study for men who have sex with men. The receptionist will ask each male client to read the flyer and to visit the study research assistant who sits at a nearby desk , if they are interested in finding out more about the study.
2. Those male clients who express interest in participating will see the study research assistant, who will take them to a private clinic room where an iPad questionnaire system is installed.
3. The study research assistant will explain what the study involves and go through the iPad-based full Participant Information and Consent Form (PICF) with potential eligible participants. Participants will have time to read the PICF, to ask questions, and to decide if they will participate in the study.
4. The study research assistant will ask consented participants to complete the iPad-based questionnaire on their own, in the private room. They will be instructed that if they have any further questions, they should ask the research assistant who will be at a desk, outside of the private room.
5. The pre-programmed logic in the questionnaire will judge if a participant is actually eligible, based on sexual behavior variables. Eligible participants will provide a valid mobile phone number and then be automatically randomised into either intervention or control group, by the computer. Those who are not eligible will be thanked and released back into the clinic waiting room for their routine clinical care.
6. Eligible participants will see the study research assistant who guides them to see a doctor for biospecimen collection, followed by routine clinical care, if necessary.

Figure 1. Flow chart of recruitment



Randomization: Once the participants have completed the questionnaire and judged eligible by the pre-programmed computer logic they will then be randomized by computer to either intervention group (with monthly reminders) or control group (without monthly reminders). MSM who opt out of the study will be recorded and asked about reasons to decline.

Intervention: Intervention is a monthly SMS reminder. We acknowledge that directly mentioning of sensitive words such as HIV and STIs in SMS reminders may lead to the exposure of privacy of participants to others. As a result, we will avoid using these sensitive words in actual SMS reminders.

Instead, in actual reminders we will use "***Little A***" to refer to "HIV", "***Little B***" to refer to "STIs", "***Health check***" to refer to "HIV/STI testing" and "***Self health check***" to refer to "HIV self-testing at home". We will clarify this in the PICF so participants for they to consent.

Group A: MSM in the Intervention Group

For MSM in the Intervention Group, upon enrolment, they will receive **Message A**: "A gentle reminder: If you plan to have a ***health check*** again in the next 12 months, welcome to our center. If you do it elsewhere (including ***self-health check***) in the next 12 months, please register the results online at the following link: ******. Every time you register we will compensate you with an electronic mobile phone credit of CNY10 (USD1.5). If you change your mobile phone number in the next 12 months please let us know." When they register online, participants need to enter the mobile phone number that was validated at enrolment and the initial of their surname to enter the questionnaire. This is designed to avoid the exposure of sensitive questions to a non participant. On the second day after enrolment, they will receive **Message B**: "A gentle reminder: ***Little A*** and ***little B*** are spreading rapidly and it's hard to detect by yourself. Your best protection is a regular ***health check*** (e.g. every 3 months). If you change your mobile phone number please let us know." Starting from day 30, they will receive **Message C** every 30 days: "A gentle reminder: If you have not had a ***health check*** in the past 3 months please do so as soon as possible. If you change your mobile phone number please let us know." On day 190, 10 days after they receive **Message C** on day 180, they will receive **Message D**, reminding them to complete an online survey about their sexual life and testing behaviors in the past 6 months: "A gentle reminder: please complete a survey at the following link at your earliest convenience: ******. We will compensate you with an electronic mobile phone credit of CNY50 (USD8). If you change your mobile phone number please let us know." On day 370, 10 days after they receive **Message C** on day 360, they will receive **Message E**, reminding them to complete an onsite survey about their sexual life and testing behaviors in the past 6 months: "A gentle reminder: please attend our center to complete the final survey. We will compensate you with an electronic mobile phone credit of CNY100 (USD16), together with condoms, lubricant and health booklets. If you change your mobile phone number please let us know." At enrollment and 12 months men will be tested for HIV, syphilis, urethral and anal chlamydia and gonorrohea, and examined for anogenital warts. CD4+ testing will be provided for men diagnosed with HIV. HIV/STIs will be treated as per relevant treatment guidelines in China. At 6 and 12 months men will also be asked questions about their experience of the intervention including the impact of the intervention on their everyday life, mental health, sexual health and general health (Figure 2).

Group B: MSM in the Control Group

MSM in the Control Group will receive **Message A** upon enrolment, **Message D** on day 190 and **Message E** on 370. They will not receive **Messages B** and **C**. They will complete the same questionnaire as men in the intervention group do at enrolment, 6 months and 12 months and test for above-mentioned HIV/STIs at enrolment and 12 months. They will not be asked about their experience of the intervention.

The 10 days' time gap between **Messages C** and **D** is planned to give men in both groups enough time to attend a SHC upon receiving **Message C**. Besides men's mobile phone number (compulsory) we will also try to collect other contact information (optional), including email, QQ and WeChat ID (instant online messaging applications frequently used in China). At 6 and 12 months, men will be contacted with the additional contact information if they do not complete a designated survey within 7 days after **Messages D** and **E** are sent. Men who register testing information online or fill in an online questionnaire at 6 months will need to enter their mobile number to access the actual questionnaire. This is designed in case another person oversees the URL address from **Message A**.

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Collection and storage of biospecimen samples: For men in both groups, at enrolment and 12 months, a study nurse will collect a swab from the anal canal to test for anal gonorrhea and chlamydia, and 10 ml of blood to test to test for HIV and syphilis. Participants will self-collect a urine sample to test for urethral gonorrhea and chlamydia. Biospecimen collected at a given site will be stored at the corresponding participatory institution. The biospecimen will be stored for 5 years and then disposed of.

The process from commencing CASI to the regular dispatch of the reminders will be entirely automated, requiring no human input. This study has been registered at the Chinese Clinical Trial Registry (www.chictr.org/en) and WHO International Clinical Trials Registry Platform (apps.who.int/trialsearch), ID: ChiCTR-IOR-16009304.

4. Sample Size (Maximum of 250 Words)

Outline the intended sample size for the project and justify how this will meet the aims of the study.

Power/sample size

We used the following formula to calculate sample size:

$$n = \frac{(Z_\alpha \sqrt{2\overline{pq}} + Z_\beta \sqrt{p_0 q_0 + p_1 q_1})^2}{(p_1 - p_0)^2}$$

In this formula, Z_α and Z_β represent the Z boundaries under the standard normal distribution; p_1 and p_0 represents proportion of a parameter in the intervention group and control group, respectively; p equals to the average of p_1 and p_0; q=1-p. We used 2 parameters in the calculation of sample size: (a) proportion of men who have HIV testing during the 12 months after baseline; (b) proportion of men who have condomless anal sex during the 12 months after baseline. We assumed a two-sided hypothesis test with a 5% significance level ($Z_{\alpha/2}$=1.96), a desired power of 90% (Z_β=1.28), and that both groups will have the same number of observations.

Using parameter (a), the rate of HIV testing in the past 12 months among MSM in Wuxi in 2014 was 50% (p_0), and this figure was expected to increase to 65% (p_1) according to a before-and-after study in Australia [17]. This resulted in a sample size of 225 in each group. Khosropour et al., retained around 70% of MSM for 12 months using bimonthly follow-up surveys through text messages [31]. We will adopt a number of strategies to minimize the loss-to-follow-up rate: educating investigators about the culture in MSM community and develop rapport with participants; verifying mobile number at enrolment; contacting participants on days 190 and 370 using various messaging softwares/apps such as WeChat, QQ, email, etc; and reasonable incentives. Considering a loss-to-follow-up rate of 30%, a sample size of 300 MSM in each group will be needed.

Sample size calculations tools can be found online at:

- http://powerandsamplesize.com/Calculators/ (quantitative)
- http://stat.ubc.ca/~rollin/stats/ssize/index.html (quantitative)
- http://eprints.ncrm.ac.uk/2273/4/how_many_interviews.pdf (qualitative)

5. Research Participants (Maximum of 500 words)

Describe the characteristics of the participants that you intend to recruit in the study (e.g. inclusion/exclusion criteria, sex, age range of participants).

Inclusion criteria:

1) anatomical men aged 18 years or older;
2) having over 2 male anal sex partners, or condomless anal sex with a casual male sex partner, or an STI history, in the past 12 months;
3) possessing a mobile phone;
4) willing to provide informed consent for the collection of demographics, sexual behaviors and HIV/STI testing experiences and biological samples to test for HIV/STIs;
5) residing in a study city in the next 12 months or visiting a study city frequently enough to participate

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in the study;
6) willing to register testing results if they test elsewhere during the study.

6. Recruitment of participants

Outline the methods that will be used to recruit participants to the study. The methods in this section should describe:

- What process(es) will be used to identify potential participants;
- How initial contact will be made with potential participants;
- How participants will be screened to ensure they meet the inclusion criteria.

At baseline, all male clients will be give an information flyer by a receptionist who is not directly involved in the study. The flyer includes the basic information about the study. Participants will then read the information, decide whether they might meet the inclusion criteria and decide whether they would like to participate. Potentially eligible participants who are willing and able to participate will be guided by the receptionist to a private clinic room where they will see the full Participant Information and Consent Form (PICF) for the study on an iPad. The full PICF includes the background and procedure of study, including randomization of participants (monthly reminders in one group and no reminder in the other group). At this stage men will be informed that they may or may not be eligible to participate in this study. Men will need to click the "Agree" button to consent before completing an iPad-based questionnaire. The questionnaire collects information on sexual behaviours, HIV/STI testing behaviours and diagnosis history and alcohol/tobacco/drug use. Based on the questionnaire, the pre-programed computer system will judge if a man is eligible. Eligible MSM are those who report over 2 anal sex partners, or condomless anal sex with a casual sex partner, or an STI history, in the past 6 months. Eligible MSM who are willing to participate in the study will be asked to provide a valid mobile phone number that will be verified by a code automatically sent to his phone as a short message, to participate in the trial. Men will then receive a text message with a code as their Study ID. Eligible MSM will then be randomized by pre-programed computer system to either intervention group or control group. After these steps, our research assistant will take eligible participants to see a doctor for biospecimen collection, followed by routine clinical care, in necessary. Eligible MSM who opt out of the study will be recorded and asked about reasons to decline.

7. Consent

Provide a detailed description of the consent process to include the following:

- The type of consent that will be sought (e.g. verbal/ written/ return of survey etc.), how and when you will provide consent materials to your potential participants and why this method of consent is appropriate for the participant population.
- How, when and to whom participants will indicate their consent and how any real or perceived coercion will be avoided during the consent process.

**if the project involves the use of data already collected and the participants have already provided their consent for this to happen, please attach a copy of the original consent form as evidence.
**if you are seeking a waiver of consent, please provide justification. (See the National Statement, Chapters 2.2 and 2.3 for more information).

A participant is considered as "consented" if he clicks the "agree" button to participate in the study after reading the PICF on the iPad screen, at baseline. The computer system will record this step. An electronic copy of the consent form will be sent to a participant upon request. This procedure is designed to avoid sensitive content mentioned in the consent form (such as HIV testing) to be seen by others on a paper-based PICF. An electronic copy of the consent form is less likely to be seen by others.

We acknowledge that directly mentioning of sensitive words such as HIV and STIs in SMS reminders may lead to the exposure of privacy of participants to others. As a result, we will avoid using these sensitive words in actual SMS reminders. Instead, in actual reminders we will use "***Little A***" to refer to "HIV", ***"Little B***" to refer to "STIs", "***Health check***" to refer to "HIV/STI testing" and "***Self health check***" to refer to "HIV self-testing at home". We will clarify this in the PICF so participants for they to consent.

8. Reimbursement of Expenses or Incentives to Participate

Explain whether there will be any reimbursement of out-of-pocket expenses, financial incentive or other "reward" as a result of participation in the study.

Participants will receive health education materials, condoms and lubricant upon completion of the CASI

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questionnaire at enrolment and 12 months. Participants will receive an electronic mobile phone credit of CNY50 (USD8), CNY50 (USD8) and CNY100 (USD16), upon completion of the surveys at enrolment, 6 months and 12 months. Participants who test elsewhere will receive an additional electronic mobile phone credit CNY 10 (USD 1.5) each time they register testing results online. These reimbursements are designed to compensate participants' time to participate in the study. The minimum hourly pay in the three study cities is approximately CNY20 (USD3).

9. Risks to participants

Describe the anticipated risks to the participants, including:

- Whether the benefits outweigh the risks to the participants;
- How will you manage or minimise the risks to participants.

We do not anticipate any significant harm from participating from this project. Some men will be diagnosed with HIV and/or STIs, and this may have an emotional impact however we will refer them to standard treatment and care if necessary.

Men will be asked to answer sensitive and detailed questions about their sexual behaviours however they will be informed about this in the consent form.

10. Privacy and Confidentiality

Outline the methods that will be applied to ensure that the privacy of participants is protected during:

- The recording and analyses of data;
- The storage of data;
- Publishing or reporting the information.

All electronic questionnaires, consent forms will be stored in a computer at the information center at GCSDSC as per its common practice. Biospecimen collected at a given site will be stored at the corresponding participatory institution. Data will be entered into a pre-established database with identifiable variables decoded. Data will be shared participatory institutions. Data transfer will be conducted as per data transfer standard operation procedures of both institutions.

Storage of data - China

All electronic questionnaires, consent forms will be stored in a password-protected computer at the information center at the Guangdong Provincial Center for Skin Disease and STI Control as per its common practice. The data will be stored in a format that is identifiable. This is designed to match data with individual participants in follow-up visits in this study. However, only the custodian Mr Yunyun Zhu at the Guangdong Provincial Center for Skin Disease and STI Control will have access to the original data. All identifying variables, including name (a pseudonym is ok), initial of participant's surname, mobile phone number and date of birth, will be de-identified before data are transferred to a data analyst in this study. The custodian will ensure that data is stored and managed appropriately and according to the relevant privacy laws. The data custodian will only share data with researchers who are conducting HIV/STI testing related epidemiologic studies and only once these projects have received separate ethics approval from a Human Research Ethics Committee. All identifying variables, including name (a pseudonym is ok), initial of participant's surname, mobile phone number and date of birth, will be de-identified before data sharing. Data will be stored for a period of 5 years and it will then be destroyed. Biospecimen collected at a given site will be stored at the corresponding participatory institution. The T2T Study steering committee will share specimen with future researchers only if they get ethics approval from a valid IRB committee. Samples will be de-identified when sharing with other researchers.

Storage of data - Australia

The data will be transferred to UNSW within 6 months after the final survey of the last participant is completed. The data will be stored in a password-protected computer at the HIV Epidemiology and Prevention Program at the Kirby Institute. Dr. Huachun Zou will be the custodian for this data. These data will be destroyed when the data stored in China is destroyed. Biospecimen will not be transferred to Australia.

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De-Identification of Data

The individually identifiable variables in the T2T Study include name (a pseudonym is ok), initial of participant's surname, date of birth, patient ID, mobile phone number, QQ number, WeChat ID, email address. In the analysis in the T2T Study, date of birth is required to calculate age, time since first sex, time since last HIV testing, etc. Other identifiable variables are required to match data and contact participants. For future research purposes, only age in years and Study ID will be provided, none of the other identifying variables will appear in the data transferred to other researchers.

Collection and storage of data for future research purposes (Biospecimens and Samples)
(a) Data to be stored for research purposes the information should detail the following:
Detailed procedure for data storage is described in Section 10.

(b) Access to the data for future research purposes, the information provided in this section will need to specify:
For future research purposes, researchers will need to obtain ethics approval and submit a concept sheet detailing the purpose of study and variables required. The request to access data will be reviewed by the steering committee of the T2T Study. The T2T Study steering committee will share specimen with future researchers only if they get ethics approval from a valid IRB committee. In future data sharing, samples will be de-identified and only Study ID will be provided.

11. Publications and Dissemination of Results

In this section detail how:

- The research results will be reported to the participants of the study;
- How the research results will be reported/ published;
- How participant confidentiality will be maintained in your reports and/or publications.

HIV/STI testing results will be reported to participants as per HIV/STI testing and treatment guidelines in China. The research data will be aggregated, analysed and published in academic journals and presented at national and international academic conferences. The name and any other identifying variable of individual participants will not be included in any published or publicly-available data.

Sample patient information and consent form

1. **What is the research study about?**
Over 7% of men who have sex with men (MSM) in China have been infected with HIV, with over 10% infected with syphilis and over 30% infected with gonorrhea, condyloma and other sexually transmitted infections (STIs). You are cordially invited to a participate in a study about HIV/STI testing, jointly conducted by Guangdong Provincial Center for Skin Disease and STI Control, Wuxi Municipal Center for Disease Control and Prevention, Shenzhen Nanshan Center for Chronic Disease Control and Prevention, Sun Yat-sen University and the University of New South Wales. This study aims to understand if automated short message service (SMS) reminders can lead to frequent testing and early diagnosis/treatment among MSM. Your participation will help us to improve HIV prevention strategy for the MSM community.

If you are eligible and willing to participate in this study, you will need to provide a valid phone number that will be verified by a code sent to you via SMS. Participants will be randomly allocated into two groups: one group will receive a testing reminder via SMS every 30 days, while the other group will not receive any reminder.

2. **Inclusion/Exclusion Criteria**
Before you decide to participate in this research project, we need to ensure that it is ok for you to take part. If you have ever had a male sex partner you may be eligible to participate in the study. Your eligibility will be judged by the logic pre-programmed in the questionnaire that you will see, if you agree to participate.

3. **Do I have to take part in this research study?**
Participation in any research project is voluntary. If you do not want to take part, you do not have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.
If you decide you want to take part in the research study, you will be asked to:
- Read the information carefully (ask questions if necessary);
- If you would like to participate, sign the consent form;.

4. **What does participation in this research require, and are there any risks involved?**
If you are eligible and decide to take part in the research study, you will be randomly assigned to either **Group A** (receive monthly reminders to remind you to test for HIV/STIs) or **Group B** (no monthly reminders). We will ask you to complete the following tasks:

[Completion of Questionnaires]

Today, the research team will ask you to complete an iPad-based questionnaire. This questionnaire will ask you questions about your socio-demographic characteristics, sexual behaviours, HIV/STI testing and diagnosis experiences, attitudes towards HIV pre-exposure prophylaxis, blood donation experiences, and geo-social networking app use experiences. It should take approximately 15 minutes to complete.
At 6 months, the research team will ask you to complete another online questionnaire. This questionnaire will ask you questions about your experiences in the past 6 months, including sexual behaviours, HIV/STI testing and diagnosis experiences, blood donation experiences, and geo-social networking app use experiences. It should take approximately 10 minutes to complete.

At 12 months, the research team will ask you to come back to this site to complete another iPad-based questionnaire. This questionnaire will ask you questions about your experiences in the past 6 months, including sexual behaviours, HIV/STI testing and diagnosis experiences, blood donation experiences, and geo-social networking app use experiences. It should take approximately 10 minutes to complete.

If you are assigned to **Group A**, at 6 and 12 months you will also be asked questions about your experience of the monthly reminders including the impact of the intervention on

your everyday life, mental health, sexual health and general health. You will not be asked these questions if you are assigned to **Group B**.

We don't expect these questionnaires to cause any harm or discomfort, however if you experience feelings of distress as a result of participation in this study you can let the research team know and they will provide you with assistance. Alternatively lists of services are provided in the contact details below to assist you if necessary.

[Collection of biospecimen]
Today, a study nurse will collect the following biospecimen from you: an anal swab, a urine sample and 10ml of blood sample. A doctor will also check ano-genital warts for you. It should take approximately 20 minutes to complete.

At 12 months, in the last survey, the research team will ask you to come back to this site. Besides a questionnaire, a study nurse will collect the following biospecimen from you: an anal swab, a urine sample and 10ml of blood sample. A doctor will also check ano-genital warts for you. It should take approximately 20 minutes to complete.

[HIV/STI testing]
Today and at 12 months when you come to this site for the last onsite survey, you will be tested for HIV, syphilis, urethral and anal chlamydia and gonorrohea, and examined for anogenital warts. CD4+ testing will be provided for you if you are diagnosed with HIV. HIV/STIs will be treated as per relevant treatment guidelines in China.

[SMS reminders]
We acknowledge that directly mentioning of sensitive words such as HIV and STIs in SMS reminders may lead to the exposure of privacy of participants to others. As a result, we will avoid using these sensitive words in actual SMS reminders. Instead, in actual reminders we will use "**Little A**" to refer to "HIV", "**Little B**" to refer to "STIs", "**Health check-up**" to refer to "HIV/STI testing", "**Self check-up**" to refer to "HIV self-testing at home" and "health kit" to refer to "condoms/lubes/health manuals".

If you are in **Group A**, after completion of the iPad-based questionnaire you will receive ***Message A***: "A gentle reminder: If you plan to have a health check again in the next 12 months, welcome to our center. If you do it elsewhere (including self-health check) in the next 12 months, please register the results online at the following link: ******. Every time you register we will compensate you with an electronic mobile phone credit of CNY10 (USD1.5). If you change your mobile phone number in the next 12 months please let us know." Tomorrow, you will receive ***Message B***: "A gentle reminder: ***Little A*** and ***Little B*** are spreading rapidly and it's hard to detect by yourself. Your best protection is a regular check-up (e.g. every 3 months). If you change your mobile phone number please let us know." Starting from day 30, you will receive ***Message C*** every 30 days: "A gentle reminder: If you have not had a health check in the past 3 months please do so as soon as possible. If you change your mobile phone number please let us know." On day 190, you will receive ***Message D***: "A gentle reminder: please complete a survey at the following link at your earliest convenience: ******. We will compensate you with an electronic mobile phone credit of CNY50 (USD8). If you change your mobile phone number please let us know." On day 370, you will receive ***Message E***, reminding you to complete an onsite survey about your sexual life and testing behaviours in the past 6 months: "A gentle reminder: please attend our center to complete the final survey. We will compensate you with an electronic mobile phone credit of CNY100 (USD16), together with a health kit. If you change your mobile phone number please let us know."

If you assigned to **Group B,** you will receive ***Message A*** today, ***Message D*** on day 190 and ***Message E*** on 370. You will not receive ***Messages B*** and ***C***.

You are free to withdraw from the SMS reminders by calling our study phone number at any time. You are free to withdraw from the research at any time. If you withdraw from the research we will destroy any information that has already been collected.

5. What are the possible benefits to participation?

We hope to use information we get from this research study to benefit other men who have sex with men who are at high risk for HIV/STI infection but do not test frequently enough to get diagnosed on a timely basis. You will benefit from this study with free and professional HIV/STI counselling and testing services, referral and treatment services if applicable. You will also get free condoms, lubricant and health manual.

6. What will happen to information about me?

By signing the consent form you consent to the research team collecting and using information about you for the research study, if you are eligible and willing to participate in this study. If you provide your permission the research team will store your data in a password-protected databank for 5 years. The data will be stored in a format where you will be identifiable. This is designed to match your data with you in follow-up visits in this study. However, only the custodians listed in the table above will have access to your original data. All identifying variables, including the initial of your surname, mobile phone number and date of birth, will be de-identified before data are transferred to a data analyst in this study. The custodians listed in the table above will ensure that your data is stored and managed appropriately and according to the relevant privacy laws. The data custodian will only share your data with researchers who are conducting HIV/STI related epidemiologic studies and only once these projects have received separate ethics approval from a Human Research Ethics Committee. All identifying variables, including initial of your surname, mobile phone number and date of birth, will be de-identified before data sharing.

7. How and when will I find out what the results of the research study are?

The research team intend to publish and report the results of the research study in a variety of ways, including academic conferences and journals. All information published will be done in a way that will not identify you. If you would like to receive a copy of the results you can let the research team know by adding your email within the consent form. We will only use these details to send you the results of the research. The results will also be made available via the school's website: kirby.unsw.edu.au.

8. What if I want to withdraw from the research study?

If you do consent to participate, you may withdraw at any time. You can do so by completing the 'Withdrawal of Consent Form' which is provided at the end of this document. Alternatively you can ring the research team and tell them you no longer want to participate. If you decide to leave the research study, the researchers will not collect additional information from you. Your decision not to participate will not affect your relationship with the Guangdong Provincial Center for Skin Disease and STI Control, the Wuxi Municipal Center for Disease Control and Prevention, the Nanshan District Center for Chronic Disease Control and Prevention, the Kirby Institute, University of New South Wales, and the Sun Yat-sen University, Guangzhou

9. What type of data will be stored in this data bank?

With your permission we would like to store the following types of data with the intention to share it and use it in future research projects.

- Socio-demographic characteristics, including your name (a pseudonym is ok), initial of your surname, mobile phone number, date of birth, ethnicity, marital status, educational level, income and profession.
- Sexual behaviours, including anal sex with men and vaginal sex with women and condom use during these sex.
- HIV/STI testing and diagnosis experiences
- Attitudes towards HIV pre-exposure prophylaxis
- Blood donation experiences
- Geo-social networking app use experiences
- Bio-specimen to test for HIV and other STIs

10. What will happen to my data?

If you provide your permission the research team will store your data in a

password-protected databank. The data stored in a format where you will be identifiable. This is designed to match your data with you in follow-up visits in this study. However, only the custodians listed in the table above will have access to your original data. All identifying variables, including name (a pseudonym is ok), initial of your surname, mobile phone number and date of birth, will be de-identified before data are transferred to a data analyst in this study.

11. Who will have access to my data?

Only the custodians listed in below will ensure that your data is stored and managed appropriately and according to the relevant privacy laws. The data custodian will only share your data with researchers who are conducting HIV/STI testing related epidemiologic studies and only once these projects have received separate ethics approval from a Human Research Ethics Committee. All identifying variables, including name (a pseudonym is ok), initial of your surname, mobile phone number and date of birth, will be de-identified before data sharing.

Data Custodians	*Mr. Yunyun Zhu*	*Guangdong Provincial Center for Skin Disease and STI Control, China*

12. How long will you store my data for?

We intend to store your data for 5 years. After 5 years, the data from the questionnaire will be deleted from the computer system and biospecimen will be disposed of as per biosafety practice in China.

13. Can I withdraw my information from this databank?

If you no longer wish to have your data stored or do not wish to be contacted for research purposes you can withdraw your information by completing the withdrawal of consent form that is attached or by phoning the data custodian and letting them know.

14. What should I do if I have further questions about my involvement in the research study?

The person you may need to contact will depend on the nature of your query. If you want any further information concerning this project or if you have any problems which may be related to your involvement in the project, you can contact the following member/s of the research team.

15. Research Team Contact Details

Name	*Dr. Huachun Zou*
Position	*Research Fellow*
Telephone	*+61 2 9385 3132 or +86 20 8733 5651*
Email	*hzou@kirby.unsw.edu.au*

16. Support Services Contact Details

We don't expect this study procedure to cause any distress, however if you experience feelings of distress as a result of participation in this study you can let the research team know and they will provide you with assistance. If at any stage during the project you become distressed or require additional support from someone not involved in the research please call:

Name/Organisation	*Dr. Weiying Chen/T2T Project*
Position	*Research Assistant*
Telephone	*189 2249 3020*
Email	T2TStudy@outlook.com

What if I have a complaint or any concerns about the research study?

If you have any complaints about any aspect of the project, the way it is being conducted, then you may contact:

Complaints Contact

Position	Human Research Ethics Coordinator
Telephone	+ 61 2 9385 6222
Email	humanethics@unsw.edu.au
HC Reference Number	HC16803

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Reported on page No
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	2
Protocol version	3	Date and version identifier	6
Funding	4	Sources and types of financial, material, and other support	21
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	21
	5b	Name and contact information for the trial sponsor	21
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	21

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-6
	6b	Explanation for choice of comparators	4-6
Objectives	7	Specific objectives or hypotheses	7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7-8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10-11

	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	13
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	14-17
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	8
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	13-14
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	8

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	10
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	17-18
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	17-18

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	17-18
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	15
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	16-17
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	15
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	17-18
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	18
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	N/A
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	18

Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	19
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8-9
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	27
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	17-18
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	21
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	18
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	18
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	18

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	27
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	12

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

Correction: A randomised controlled trial to evaluate the impact of sexual health clinic based automated text message reminders on testing of HIV and other sexually transmitted infections in men who have sex with men in China: protocol for the T2T Study

Zou H, Meng X, Grulich A, *et al*. A randomised controlled trial to evaluate the impact of sexual health clinic based automated text message reminders on testing of HIV and other sexually transmitted infections in men who have sex with men in China: protocol for the T2T Study. *BMJ Open* 2017;**7**:e015787. doi: 10.1136/bmjopen-2016-015787

HZ and XM contributed equally to the manuscript and are co first authors. Author name Jinmei Han should be Jinmei Huang.

BMJ Open 2017;**7**:e015787corr1. doi:10.1136/bmjopen-2016-015787corr1