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# Novel education-based intervention to reduce inappropriate antibiotic prescribing for treatment of gonorrhoea in China: protocol for a cluster randomised controlled trial

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## ABSTRACT

**Introduction** Inappropriate use of antibiotics to treat gonorrhoea can lead to antibiotic resistance. Education programmes may be helpful for improving physician prescribing behaviours in accordance with treatment guidelines. As traditional education based on printed materials may have limited effect on guideline-based treatment, innovative education strategies are needed. The current trial aims to assess the effectiveness of a novel education intervention to increase guideline-based treatment of gonorrhoea in China.

**Methods and analysis** We will conduct a two-arm cluster randomised control trial at 144 hospitals (clusters) in eight Chinese provinces. The intervention will include an online training video developed on the WenJuanXing platform that covers workflows and requirements for managing a patient with uncomplicated gonorrhoea. Outpatient physicians in dermatology (dermatovenerology), urology, andrology and gynaecology will be given access to the video via a quick response code. In hospitals allocated to the control arm, physicians will continue to participate in their standard of care training programme. The primary outcome is the proportion of gonorrhoea antibiotic prescriptions adherent to Chinese national guidelines at the cluster level. In addition, to understand the reasons of physician's non-adherence to the intervention by conducting a questionnaire survey will be considered as the secondary outcome of the study.

**Ethics and dissemination** Ethical approval was obtained from the Medical Ethics Committee of the Chinese Academy of Medical Sciences Institute of Dermatology (2020-LS-004). All physicians will provide an informed consent prior to participating in the study. Findings of the trial will be disseminated through conferences and peer-reviewed journals, and will be used to develop training programmes for physicians.

**Trial registration number** ChiCTR2000029591.

## Strengths and limitations of this study

- The study design (cluster randomised controlled trial) is a robust methodology to assess the effectiveness of behavioural interventions.
- The study will be carried out in eight different provinces in China, thus will provide insights on whether the intervention can be implemented in different local contexts.
- The questionnaire administered to physicians prior to the intervention may influence the prescribing behaviours of physicians from hospitals in the control arm, which may undermine the effect of intervention.

## INTRODUCTION

Gonorrhoea, caused by *Neisseria gonorrhoeae*, remains one of the most common sexually transmitted diseases (STDs) worldwide. According to the most recent WHO report in 2016, there were 86.9 million incident cases (15–49 years of age) globally, which were more than 10% higher than that in 2012.[1] Left untreated, the infection can cause serious medical problems, particularly for women, including chronic pelvic pain, ectopic pregnancy and even infertility.[2] In addition to the behavioural interventions to prevent infection of gonorrhoea, timely detection of the infection followed by effective treatment with antibiotics remains the mainstream strategy to control this infection. Unfortunately, *N. gonorrhoeae* has developed resistance to nearly every antibiotic ever used to effectively treat it since sulphonamides were introduced as the first drugs for this treatment in 1940s.[3] Due to widespread emergence of the resistant strains, only the extended-spectrum cephalosporin (ESC) and azithromycin which is usually used with ceftriaxone in dual therapy are left to be recommended as first-line regimen for treatment of gonorrhoea in most countries.[4–7] However, in recent years, gonococcal strains with reduced susceptibility or resistance to ESC and resistance to high-level azithromycin

have been identified from many countries including China.[8 9] Treatment failures with ceftriaxone have been reported in Japan, Australia, European countries, Canada and South Africa.[10–13] Data from the China Gonococcal Resistance Surveillance Programme indicated that 18.6% of clinical isolates were resistant to azithromycin and 9.7%–12.2% of clinical isolates were less susceptible to ceftriaxone over the years of 2013 and 2016.[14]

It has been recognised that much of the antimicrobial resistance (AMR) of gonorrhoea originates in Asia and then transmitted to the rest of world.[15 16] Although many factors contribute to the emergence of gonococcal AMR, inappropriate use (misuse or overuse) of antibiotics for treatment of gonorrhoea in clinical practice in many countries in Asia may be one of drivers for AMR due to antibiotic selective pressure. A recent study in China indicated less than 1% of patients with uncomplicated gonorrhoea were treated following the ceftriaxone regimen recommended by the national guidelines (ceftriaxone 250 mg intramuscular as a single dose).[17] More than 70% of the patients received a dosage of more than 1 g for their treatment.[17] Several factors affect physicians' prescribing behaviours, including knowledge about the antibiotics, awareness of national guidelines, previous experience in treatment and trust to the antibiotics. A nationwide survey in China revealed a higher adherence to the national guidelines for treatment of uncomplicated gonorrhoea among physicians who were aware of the guidelines than those who were not. Additionally, participation in training courses did not significantly improve the prescribing behaviours of physicians,[18] indicating that more innovative interventions are needed to address the issues of inappropriate antibiotic use in treatment of gonorrhoea in China. Exploring innovative strategies to ensure appropriate use of antibiotics for treatment of gonorrhoea has been listed as one of the priorities in a comprehensive research plan called ROADMAP (resistance surveillance, outcomes due to AMR, antibiotic stewardship and application, diagnostic tools, mechanisms of AMR, antimicrobial assessment and population pharmacokinetics and pharmacodynamics) to address research needs for gonococcal AMR in China.[19]

Mobile health (mHealth), defined as interventions and programmes designed to support medical and public health through the use of mobile technology, has been used as a tool to deliver continuous training and education to healthcare providers.[20 21] Previous randomised controlled trials (RCTs) have shown success of mHealth in optimising antibiotic prescribing.[22–24] However, there has been no studies to shine a light on whether such training programme is beneficial to improve antibiotic prescribing behaviours among physicians who provide treatment to patients with STDs. For this purpose, we will conduct a cluster randomised trial to evaluate whether the proposed intervention (online video-based training programme) could significantly improve physicians' prescribing behaviours to adhere to the regimens for treatment of uncomplicated gonorrhoea (1 g intramuscular ceftriaxone single dose) recommended by the National STD Treatment Guidelines[25] (hereinafter referred to the National Guidelines). Our secondary objective is to understand the reasons of physicians' non-adherence to the online video-based training programme.

## METHODS AND ANALYSIS

### Study design and setting

We will use a parallel-group, cluster-RCT with one intervention and one control arm, using a 1:1 allocation ratio, to evaluate whether the intervention is superior to the control treatment (figure 1). Selection of provinces for the study is based on the reported incidence of gonorrhoea in 2018. The eight provinces (Jiangsu, Shanghai, Zhejiang, Fujian, Guangdong, Guangxi, Hainan and Yunnan) with the highest incidence of reported gonorrhoea cases (figure 2) in China were selected. Among the eight selected provinces, Jiangsu, Shanghai, Zhejiang, Fujian, Guangdong and Hainan are in the eastern areas, while Guangxi and Yunnan are in the western areas of China. According to geographic location and level of economic development, mainland China was classified into three areas—eastern areas (high level of economic development), middle areas (middle level of economic development) and western areas (low level of economic development). In China, healthcare workers (especially highly educated physicians) usually prefer to work in more economically developed areas, which results in a severe inequality in the quantity and quality of healthcare workforce. Training is considered an important way to enhance professional skills of healthcare workers, but the effects of training may vary from area to area. Therefore, by evaluating the intervention effects in Chinese hospitals in multiple provinces, the current study may provide insights on whether the intervention can be effective across different local contexts.

Within each study province, we will invite the city-level hospitals with the highest volume of reported gonorrhoea cases to participate in the study. Hospitals at national or province-level will be excluded from the study, because there are such a small number of these hospitals that will make it difficult to ensure comparable assignments into the intervention and control arms. Hospitals will be randomised into the intervention or the control arm, stratified by province, considering the potential variation in outcomes between provinces. Core elements of the intervention are online training on antibiotic prescribing for treatment of uncomplicated gonorrhoea among physicians working in the department of dermatology (dermatovenerology), urology, andrology or gynaecology in the intervention arm hospitals. A clustered design is used to avoid the risk of contamination between different physicians within hospitals.

The study will be divided into two subtrials, that is, a pilot trial and a main trial. The pilot trial will be conducted in one province randomly selected from the eight study provinces. Data will be collected simultaneously in nine

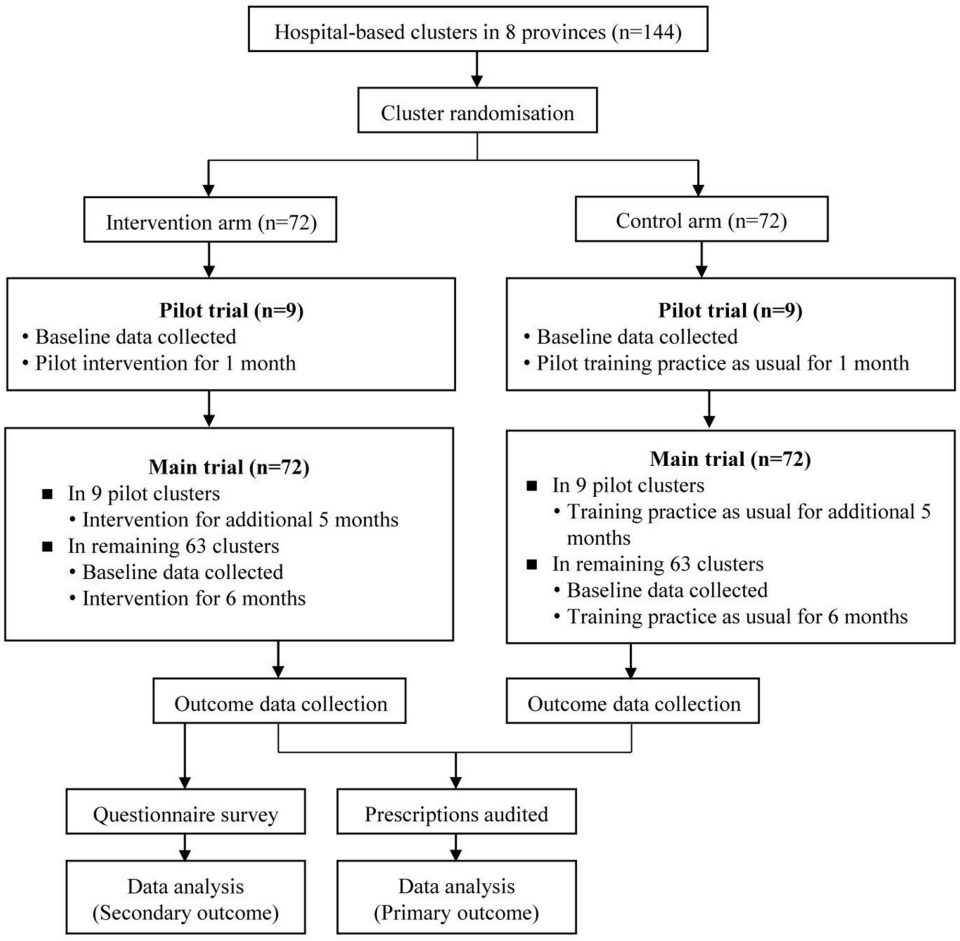


**Figure 1** Flow chart of the cluster randomised controlled trial.

intervention and nine control hospitals for a month to examine the feasibility and acceptability of the intervention. If more than 60% of physicians are willing to use the online training, the internal pilot hospitals and their outcome data will then become part of the main trial, and will be followed up for another 5 months (figure 1). The remaining hospitals will be enrolled into the main trial and followed up for 6 months (in other words, data collection in the pilot and main trial hospitals will finish at different times). An independent advisory group consisting of key investigators, a programme manager, hospital representatives and a statistician will be established to oversee the trial implementation, review the study progress and provide the corresponding advices.

## Participants, recruitment and consent

The study is planned to start in October 2020 and end by August 2021. The hospital selection and project coordinator recruitment will take place in October 2020. Baseline assessments will be carried out before randomisation between November and December 2020. The internal pilot trial will be conducted in January 2021. The intervention programme will be administered from February to July 2021 followed by a questionnaire survey in intervention hospitals in August 2021.

City-level hospitals with highest volume of reported gonorrhoea cases are eligible to participate in the study. Our investigators will prepare a list of eligible hospitals to invite to participate in each of the eight study provinces. The objectives and processes of the study will be explained to the hospital administrations and the in-hospital project coordinators. If a hospital agrees to participate in the study, the in-hospital project coordinator will work together with the study investigators to invite physicians to participate in the study. Physicians who work in the outpatient departments of dermatology (dermatovenerology), urology, andrology or gynaecology and provide informed consent (see online supplementary file 1) will be eligible to participate in the study. Prescriptions of these physicians for treatment of uncomplicated gonorrhoea will be evaluated for their adherence to the National Guidelines. Prescriptions will be excluded from data analysis if they are prescribed to the patients who meet any of the following criteria: (1) younger than 18 years; (2) being pregnant or lactating woman; (3) being allergic to cephalosporin or penicillin or having contraindication to cephalosporin; (4) being treated with antibiotics for other infections or (5) have been diagnosed as complicated gonorrhoea, such as disseminated gonococcal infection and pelvic inflammatory disease.

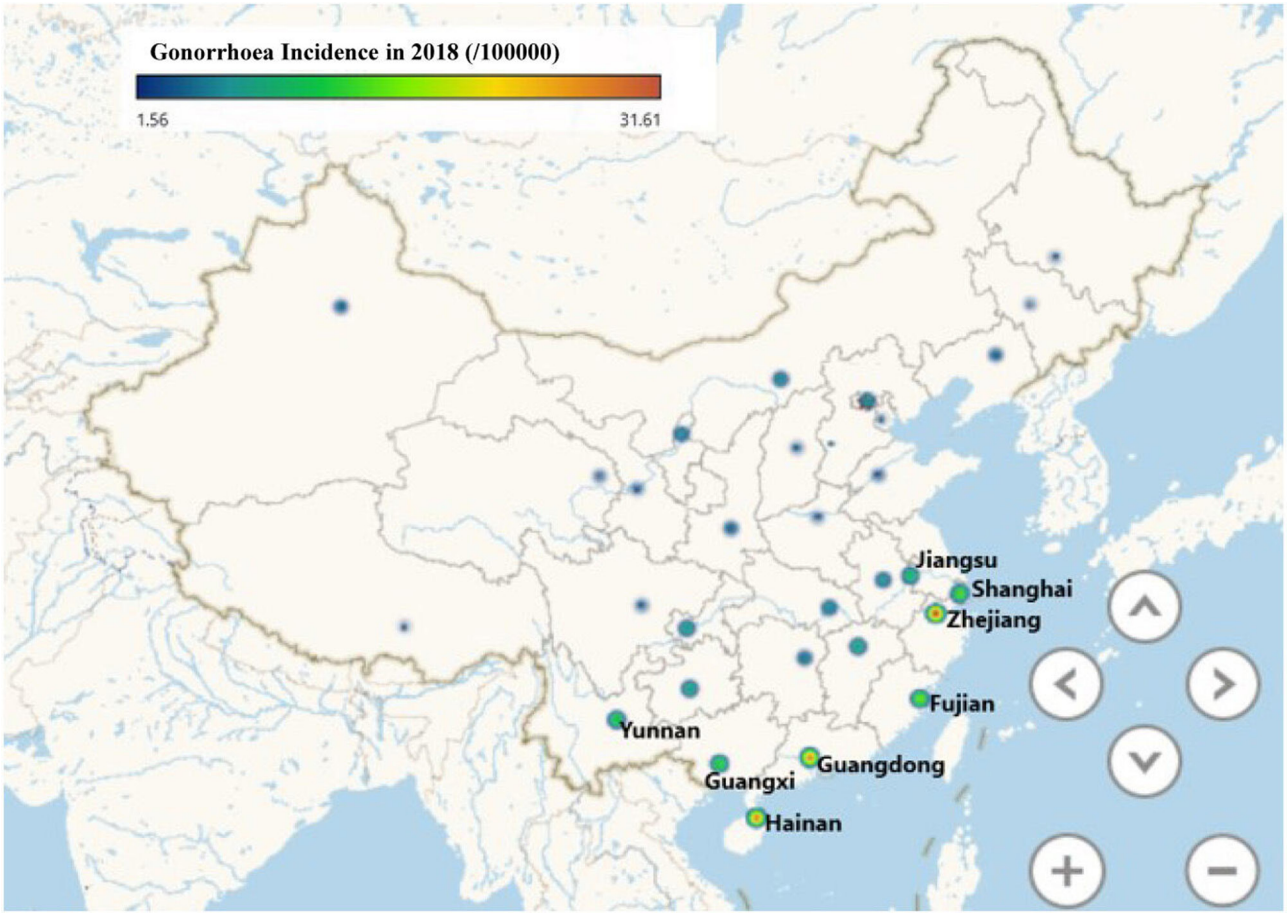


**Figure 2** Reported incidence rate of gonorrhoea in 2018 in 31 provinces, autonomous regions and municipalities in the mainland of China.

## Intervention and control

The proposed intervention to be evaluated in the study is aimed to improve the physicians' adherence to the National Guidelines by reducing inappropriate antibiotic prescribing for treatment of patients infected with *N. gonorrhoeae*. Our research team have designed an information card (figure 3) to be distributed to all participating physicians in the intervention arm hospitals by surface mail. By scanning a quick response (QR) code on the information card (figure 3), physicians will have access to an online training video developed on the internet platform of WenJuanXing (https://www.wjx.cn/). The video covers the workflows and requirements to manage a patient with uncomplicated gonorrhoea, including diagnostic criteria and treatment recommendations in accordance with the National Guidelines, and provides the contact information for inquiry related to the diagnosis and treatment.

In the intervention arm hospitals, project coordinators will provide a less than 30-minute interactive training session in each of the relevant departments (integrated within monthly department meeting) prior to the intervention to explain the information card and the way to use the QR code for accessing the online training video. The intervention will last for 6 months. During the 6 months, the project coordinators will send reminders for the video playback to participating physicians through monthly Wechat messages.

The frequency of visiting the online training video from each intervention hospital will be recorded in real-time on the WenJuanXing platform. The project manager will evaluate whether or not the intervention is delivered as intended from the server logs.

In hospitals allocated to the control arm, physicians will continue to participate in their training programme if they conventionally do it and to prescribe antibiotics for treatment of gonorrhoea cases according to their own knowledge and beliefs.

## Outcomes

The primary outcome is the proportion of prescriptions adherent to the regimens for treatment of uncomplicated gonorrhoea recommended by the National Guidelines at the cluster level, which will be documented at baseline and at final evaluation.

The secondary outcome is a physician-level binary indicator of non-adherence (defined as having at least 25% of prescriptions non-adherent to the National Guidelines).

## Sample size estimation

The minimum sample size for this study was obtained using the formula outlined below[26]:


**Figure 3** The information card with a quick response (QR) code (hosted by WenJuanXing) to be distributed to physicians in the intervention arm hospitals.

$$c = 1 + (Z_{\alpha/2} + Z_{\beta})^2[\pi_0(1-\pi_0)/n + \pi_1(1-\pi_1)/n + k^2(\pi_0^2 + \pi_1^2)]/(\pi_0 - \pi_1)^2$$

where $Z_{\alpha/2}$ is the critical value of the normal distribution at $\alpha/2$ (for a confidence level of 95%, $\alpha$ is 0.05 and the critical value is 1.96), $Z_{\beta}$ is the critical value of the normal distribution at $\beta$ (for a power of 90%, $\beta$ is 0.1 and the critical value is 1.28), $\pi_0$ and $\pi_1$ are the proportions in the control and intervention arms, respectively, n is the number of samples needed in each cluster and k is the between-cluster coefficient of variation of the proportions between clusters within each arm.

We used the following parameters and assumptions to estimate the sample size: $Z_{\alpha/2}$=1.96, $Z_{\beta}$=1.28, $\pi_0$=37.8% (based on a nationwide survey[18] in China), $\pi_1$=41.6% (based on a consultation of STD clinical experts and control programmers, a minimum 10% increase in adherence to the National Guidelines is deemed clinically relevant in the intervention arm), n=100 (minimum number of uncomplicated gonorrhoea patients per hospital within 6 months) and k=0.1 (based on a nationwide survey[18] in China).

By entering these parameter and assumptions into the above formula, it is indicated that a total of 60 hospitals per arm are needed. Considering a possibility to have 10% missing data for analysis and a necessity to do stratified randomisation, a total of 144 hospitals will be recruited in the eight provinces for the study (18 hospitals in each province).

### Cluster randomisation

Within each province, we will stratify the hospitals (clusters) into two groups (provincial capital city and other cities), and 4 hospitals from capital city and 14 hospitals from other cities will be purposively selected in consideration of the highest volume of reported cases. In each stratification, a simple randomisation process will be used to assign the hospitals into the intervention or the control arm. Thus, we will have 72 hospitals assigned to the control group and 72 to the intervention group, 9 and 9, respectively for each of the eight participating provinces. After all 144 hospitals were randomised, one province will be randomly selected from the eight participating provinces to become the internal pilot area using closed and opaque envelopes by an independent person from the research team, thus the 18 participating hospitals (nine from each arm) in this selected province will become the internal pilot clusters. The remaining 126 hospitals (63 from each arm) will, therefore, participate in the main trial, along with the 18 hospitals involved in the internal pilot (figure 1). Randomisation is conducted by an independent statistical analyst using a computer program written in R (V.3.5.3).

It will not be possible to blind either in-hospital project coordinators or participating physicians on the arm assignment, given the explicit nature of the intervention components (eg, physicians in the intervention hospitals will be trained by in-hospital project coordinators). However, the prescription assessors and the data analyst will not be aware of the assignments. Moreover, the patients will not be informed of the physician's status in the control or intervention arm.

### Data collection

Physician participating in the study will be assigned a 4-digit working number by the project coordinators, and this number will be used as an identification code in the questionnaire surveys and prescription audits. This number will only be known to the project coordinator and be used to match the questionnaire surveys and prescription audits.

Prior to implementation of the intervention, we will have a baseline survey to collect background information of the participating hospitals (see online supplementary file 2) and another baseline questionnaire survey to collect background information of the participating physicians (see online supplementary file 3) in both intervention and control groups for evaluating the appropriateness of randomisation. A specific questionnaire survey (see online supplementary file 4) will be conducted among the physicians in the intervention hospitals after implementing the intervention to collect data for measuring the secondary outcome.

Based on the Hospital Information System, our investigators (prescription assessors) will screen the prescription to obtain the most recent 100 eligible prescriptions from each participating hospital prior to intervention implementation period and 6 months after the implementation, and extract patient's characteristics, diagnosis and treatment, using a data collection form (see online supplementary files 5 and 6).

### Data analysis

The data analysis methods are described in full detail in the accompanying data collection and analysis plan (see online supplementary file 7) and are, therefore, only outlined in brief here. We will conduct a complete case analysis of outcomes unless there is an indication that data may be missing not at random, in which multilevel multiple imputation methods to deal with missingness will be employed as sensitivity analysis in addition to the complete case analysis.[27]

The characteristics of the participating hospitals (hospital level, hospital category) and the participating physicians (including sex, age, education level, working year, department and previous training) will be summarised using frequencies (plus sample sizes) and means (plus SDs) as appropriate for each group.

For the primary outcome, data at the hospital level will be used to calculate weighted rate ratios and 95% CIs (accounting for between-cluster variance and stratification), and formal hypothesis testing with stratified t-tests will be conducted.[28 29] To adjust for potentially important covariates, including individual and contextual factors, a two-stage adjusted analysis will be conducted.[29] We will fit a logistic regression model to the individual-level binary outcome data including all covariates of interest as fixed effects, but without adjusting for the treatment effect. The covariate-adjusted cluster-level ratio residuals will then be calculated and be used in place of raw cluster-level outcome data to conduct stratified t-test and calculate 95% CI using the above methods. Statistical significance will be based on the (two-sided) p value estimated for the primary outcome obtained from the covariate-adjusted analysis, considering adjusting increases power and reduces the effect of imbalances between arms with typically minimal risks. We will also conduct a subgroup analysis on the primary outcome to indicate the intervention effect across the subgroups in terms of hospitals and physicians. For the secondary outcome, we will define the physicians who have at least 25% prescriptions non-adherent to the National Guidelines as the physician with non-adherence, and then use multivariate logistic regression model to identify the independent variables associated with the non-adherence at a significant level of $p \leq 0.05$ and estimate adjusted OR and its 95% CIs by adjusting for potential confounding factors. No interim analyses are planned.

### Process evaluation

Process evaluation will be conducted by collecting real-time summary data on access to the intervention (watching the video) from the WenJuanXing platform. Based on the summary data, hospitals with poor access to the intervention will be selected to conduct qualitative interviews of the public health staff, physicians and administrative staff to discuss the factors related to the poor access at cluster level. The qualitative data will be analysed using a simple thematic approach.

### Patient and public involvement

Patients and the public were not involved in the development of the research question or outcome measures. Physicians will be invited to give feedback on their barriers to comply with the intervention during the pilot trial in order to improve the intervention.

## ETHICS AND DISSEMINATION

The study protocol has been reviewed and approved by the Medical Ethics Committee of the Chinese Academy of Medical Sciences Institute of Dermatology in Nanjing (2020-LS-004). An amendment will be submitted to the Committee for review and approval if any changes are made to the study protocol. All questionnaires, prescription audits and other data sources will be kept securely and available to authorised individuals for data analysis and reporting purposes only. Data will be entered into the database in an anonymised form to ensure

confidentiality. Only principal investigator and other authorised personnel will have access to the final study database. The findings of the trial will be disseminated through reports at the national and international conferences, at least two publications in peer-reviewed journals, and provision of evidence for developing the on-the-job training programmes for physicians who provide services to patients with STDs.

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**Contributors** X-SC: conceptualised the study. T-TJ, Y-QY and X-SC: designed the study. N-XC and Y-PY: participated in the study design. T-TJ: wrote the first draft of this protocol. X-SC: made critical revision of the study protocol. Y-QY, N-XC and Y-PY: contributed to the revision of the study protocol. All authors reviewed and approved the final manuscript.

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**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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