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A novel education-based intervention to reduce inappropriate antibiotic prescribing for treatment of gonorrhea in China: protocol for a cluster randomized controlled trial

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ABSTRACT

Introduction: Inappropriate use of antibiotics in treatment of gonorrhea in clinical practice may facilitate emergence of gonococcal antimicrobial resistance. Education programme may be helpful for improving physicians' prescribing behaviors to follow the treatment guidelines. As traditional education based on printed materials may have limited effect on the compliance, innovative education strategies are needed. The trial is aimed to assess a novel education intervention in improving compliance with the national guidelines in antibiotic prescribing for treatment of gonorrhea in China.

Methods and analysis: The study will use a cluster randomized controlled trial design to conduct for six months. Within each province, 18 hospital will be stratified firstly by hospital characteristics and then randomly allocated to either intervention or control arm (allocation ratio of 1:1). The intervention procedures will include to introduce an on-line training video on WenJuanXing platform to all physicians who work in the out-patient departments of dermatology (dermatovenerology), urology, and andrology. By scanning QR code, physicians could access to the training video. The video covers workflows and requirements for managing a patient with uncomplicated gonorrhea, and provides the contact information for inquiring any questions as well. In hospitals allocated to the control arm, physicians will continue to participate in their training programme if they conventionally do it. The primary outcome is to estimate the proportion of prescriptions adherent to the regimens for treatment of uncomplicated gonorrhea recommended by the national guidelines. The secondary outcome is to identify factors related to the nonadherence.

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) and all physicians will provide an informed consent prior to participation in the surveys. The findings of the trial will be disseminated through conferences, peer-reviewed journals, and developing training programmes for physicians.

Keywords: gonorrhea, antibiotic, prescribing behavior, education, cluster randomized controlled trial

Strengths and limitations of this study

- The study design (cluster randomized controlled trial, cluster-RCT) is a robust methodology to assess the effectiveness of behavioral interventions.
- The study will be carried out in 8 different provinces, providing potentially useful information about the extent to which implementation of the intervention is likely to be influenced by local context.
- Questionnaire survey on physicians before initiating the intervention may influence the prescribing behaviors of physicians from control hospitals, which underestimates the effect of intervention.

Trial registration number ChiCTR2000029591.

INTRODUCTION

Gonorrhea, caused by *Neisseria gonorrhoeae* (*N. gonorrhoeae*), remains one of the most common sexually transmitted diseases (STDs) worldwide. According to the most recent World Health Organization (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 behavioral interventions to prevent becoming infected with this disease, timely detection of the infection followed by effective treatment with antibiotics remain the mainstream strategy for control of 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 gonorrhea 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] and treatment failures with ceftriaxone have been reported in Japan, Australia, European countries, Canada, and South Africa.[10-13] The data from the China Gonococcal Resistance Surveillance Programme (China-GRSP) 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 recognized that much of the antimicrobial resistance (AMR) of gonorrhea 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 gonorrhea 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 gonorrhea 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 1g for their treatment.[17] Several factors affect physicians' prescribing behaviors, 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 gonorrhea among physicians who were aware of the guidelines than those who were not but the participation in training courses did not significantly improve the prescribing behaviors,[18] indicating that more innovative interventions are needed to address the issues of inappropriate antibiotic use in treatment of gonorrhea in China. To explore the innovative strategies to ensure appropriate use of antibiotics for treatment of gonorrhea has been listed as one of priorities in a comprehensive research plan called the 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] For this purpose, we will conduct a prospective cluster randomized trial with a primary objective to observe whether the intervention arm could improve the adherence rate to the national guidelines above the control arm by 10% in antibiotic prescribing for treatment of uncomplicated gonorrhea. Our secondary objectives are to identify factors related to nonadherence to national guidelines among participants in the intervention arm.

METHODS AND ANALYSIS

Study design

The study is a cluster-randomized controlled trial to pragmatically validate the superiority of an on-line video-based education intervention to the conventional practice in guiding prescribing behaviors in treatment of patients with gonorrhea. The study will be divided into two sub-trials, i.e., pilot and main trials. The internal pilot trial will be conducted in one of 8 study provinces (Jiangsu) to examine feasibility and acceptability of the intervention within the first month following the main trail for 6 months if the intervention is feasible and acceptable at the current format (more than 60% of physicians being willing to accept the intervention within a month and participate in the study) (**Figure 1**). An independent advisory group consisting of key investigators, programme manager, hospital representatives and statistician will be established to oversee the trail implementation, review the study progress and provide the corresponding advices.

Study sites

The study will be conducted in 8 provinces (autonomous regions and municipalities), including Jiangsu, Shanghai, Zhejiang, Fujian, Guangdong, Guangxi, Hainan, and Yunnan, where the reported incidence of gonorrhea is above the national average and the national sentinel site for monitoring gonococcal resistance is established (**Figure 2**).

Sample size estimation

The minimum sample size for this study was obtained using the formula outlined below.[20]

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

where $Z_{\alpha/2}$ is the critical value of the normal distribution at $\alpha/2$ (for a confidence level of 95%, α is 0.05 and the critical value is 1.96), Z_{β} is the critical value of the normal distribution at β (for a power of 90%, β is 0.1 and the critical value is 1.28); π_0 and π_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_{β} = 1.28, π_0 = 37.8% (baseline proportion of prescriptions that are adherent to the regimens for treatment of uncomplicated gonorrhea recommended by the up-to-dated National Guidelines for Management of Sexually Transmitted Diseases (hereinafter referred to the National Guidelines)),[21] π_1 = 41.6% (calculated by assuming at least 10% increase in adherence to the National Guidelines in intervention arm from the 37.8% in the control arm), n = 100, and k = 0.1.

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% loss of data from illegible prescriptions and a necessity to do stratified randomization, a total of 144 hospitals will be recruited in the 8 provinces for the study (72 each in the control and intervention arms). Within each study province, 18 hospitals, excluding national or province-level hospitals because such hospitals are believed to have incomparably better knowledge in case management than others within the province, with the high volume of reported gonorrhea cases will be invited to participate in the study.

Cluster randomization

Within each province, 18 hospitals will be stratified firstly by hospital characteristics and then randomly allocated to either intervention or control arm to ensure equal numbers of hospitals in the two study arms (allocation ratio of 1:1) (**Figure 1**). Randomization is conducted by independent statistical analysts using a computer program written in R (V.3.5.3).

Although the participating physicians are impossible to be masked to the intervention assigned to them in the trial, the data analysts will be masked to the assignments.

Eligibility for participation

Hospitals with the out-patient departments of dermatology (dermatovenerology), urology, or andrology and the storage of ceftriaxone and/or spectinomycin are eligible for participating in the study. Physicians from these departments who agree to participate in the study are eligible to have their prescriptions audited for the prescribing adherence.

Intervention and control

The proposed intervention to be validated 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*. The intervention procedures include to introduce an on-line training video developed on the WenJuanXing platform to all physicians who work in the out-patient departments of dermatology (dermatovenerology), urology, and andrology in the intervention hospitals. By scanning QR code on the information card (**Figure 3**), physicians could access to the training video. The video covers the workflows and requirements to manage a patient with uncomplicated gonorrhea, including diagnostic criteria and treatment recommendations in accordance with the National Guidelines, and provides the contact infection for enquiring any questions related to the diagnosis and treatment as well. A short interaction (usually less than 30 minutes) between a public health staff and the physicians to interpret the intervention will take place in each of the department by integrating it into the most recent monthly department meeting following the implementation of the intervention for six months. The physicians will be contacted by the public health staff every two months through WeChat to remind about video playback if necessary.

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 gonorrhea cases according to their own knowledge and believes.

Outcomes

The primary outcome is the proportion of prescriptions adherent to the regimens for treatment of uncomplicated gonorrhea recommended by the National Guidelines. Prescription adherence is defined as prescribing ceftriaxone 500 mg, or spectinomycin 2 or 4 g IM as a single dose to cases diagnosed as uncomplicated gonorrhea.[21] Adherence rate is defined as the proportion of prescriptions adherent to the National Guidelines among all prescriptions audited during baseline or evaluation surveys. To explore any reasons related to prescribing behaviors nonadherent to the National Guidelines among physicians in the intervention hospitals, the secondary outcome is to identify factors related to the nonadherence. This outcome will be helpful for improving or optimizing the current intervention programmes.

Data collection

Background information of the participating hospitals are collected using a form (**see Supplement 1**). The physicians in the participating hospitals (intervention and control hospitals) will be invited to participate in a questionnaire survey and then complete the questionnaire on-line to collect their background information if they are willing to participate (**see Supplement 2**). To collect the background information of participating hospitals and physicians is aimed to evaluate the comparability between intervention and control arms. In addition, baseline data of prescribing adherence will be retrospectively collected from the most recent 30 archived prescriptions prior to the trial in each of the departments in each of participating hospitals using **Supplement 3**.

Collection of the prescription data for evaluating the primary outcome will be initiated one month after implementation of the study and conducted monthly thereafter for at least 6 months. The prescriptions from the departments are screened to see whether they are used for treatment of uncomplicated gonorrhea. If yes, they are coded and included into a standby set for evaluation. In each hospital, around 17 prescriptions per month are randomly selected from the set to collect the prescribing information using **Supplement 4**. All prescriptions are selected if the total number of prescriptions is less than 17 prescriptions in a certain month.

To explore the factors related to the nonadherence to the National Guidelines among physicians in the intervention hospitals (to meet the secondary outcome), a survey using a structured questionnaire (**see Supplement 5**) is conducted for each physician to collect

information on socio-demographics, education background, working experience, knowledge and beliefs, training experience with the video and others, concerns on treatment, comments on the National Guidelines, and suggestions to the training programmes.

Data analysis

We will use tabular and graphical summaries to describe the background and baseline characteristics. Categorical variables will be described as prevalence rate, including prescribing adherence rates, and 95% confidence intervals (CIs) and compared between groups using the chi-squared (χ^2) test or Fisher exact test when appropriate. Numeric continuous variables will be described as mean ± standard deviation (SD) or as median (interquartile range, IQR) and compared between groups using the Student's t test or the Mann-Whitney U test depending on variable distribution. Results with p value of ≤0.05 are considered to be statistically significant.

We will analyze the crude and covariate adjusted average effect of the intervention using methods appropriate for stratified, cluster-randomized trials with small numbers of clusters per arm.[22] The crude absolute effect of the intervention on the physicians' prescribing behaviors is estimated by estimating the difference for the endline prevalence of adherence to treatment guidelines, based on a weighted average of stratum specific cluster-level endline differences, with weights inversely proportional to stratum-specific variances.[22] Formal testing of the null hypothesis will be conducted using stratified t-tests, and 95% CIs will be adjusted for between-cluster variance and stratification. Single and multiple variable regression analyses will be further conducted to identify factors related to nonadherence to the National Guidelines among participants in the intervention arm. All analyses will be on the intention-to-treat (ITT) basis.

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 for conducting 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 analyzed 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 involved during the conduct of the study by giving feedback on their barriers to comply with the intervention during the pilot trial in order to tailor 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. Physicians will provide an informed consent prior to participation in the baseline and evaluation surveys and an additional informed consent prior to auditing their prescriptions. Participating physicians will be free to withdraw from the study at any time. All questionnaires, prescription audits and other data sources will be kept securely and available to authorized individuals for data analysis and reporting purposes only. Data will be entered into the database in an anonymized form to ensure confidentiality. Only principal investigator and other authorized 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, publishing at least two papers in the peer-reviewed journals, and provision of evidence for developing the on-the-job training programmes for physicians who provide services to patients with STD.

Contributors

XSC: conceptualized the study. TTJ, YQY and XSC: designed the study. NXC and YPY: participated in the study design. TTJ: wrote the first draft of this protocol. XSC: made critical revision of the study protocol. YQY, NXC and YPY: contributed to the revision of the study protocol. All authors reviewed and approved the final manuscript.

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Disclaimer

The funders of the study had no role in the design of the trial, and writing of the study protocol, and decision on submission of the manuscript for publication.

Competing interests

None declared.

Patient consent

Not required.

Ethics approval

Ethical approval for this study was obtained from the Chinese Academy of Medical Sciences Institute of Dermatology in Nanjing (2020-LS-004).

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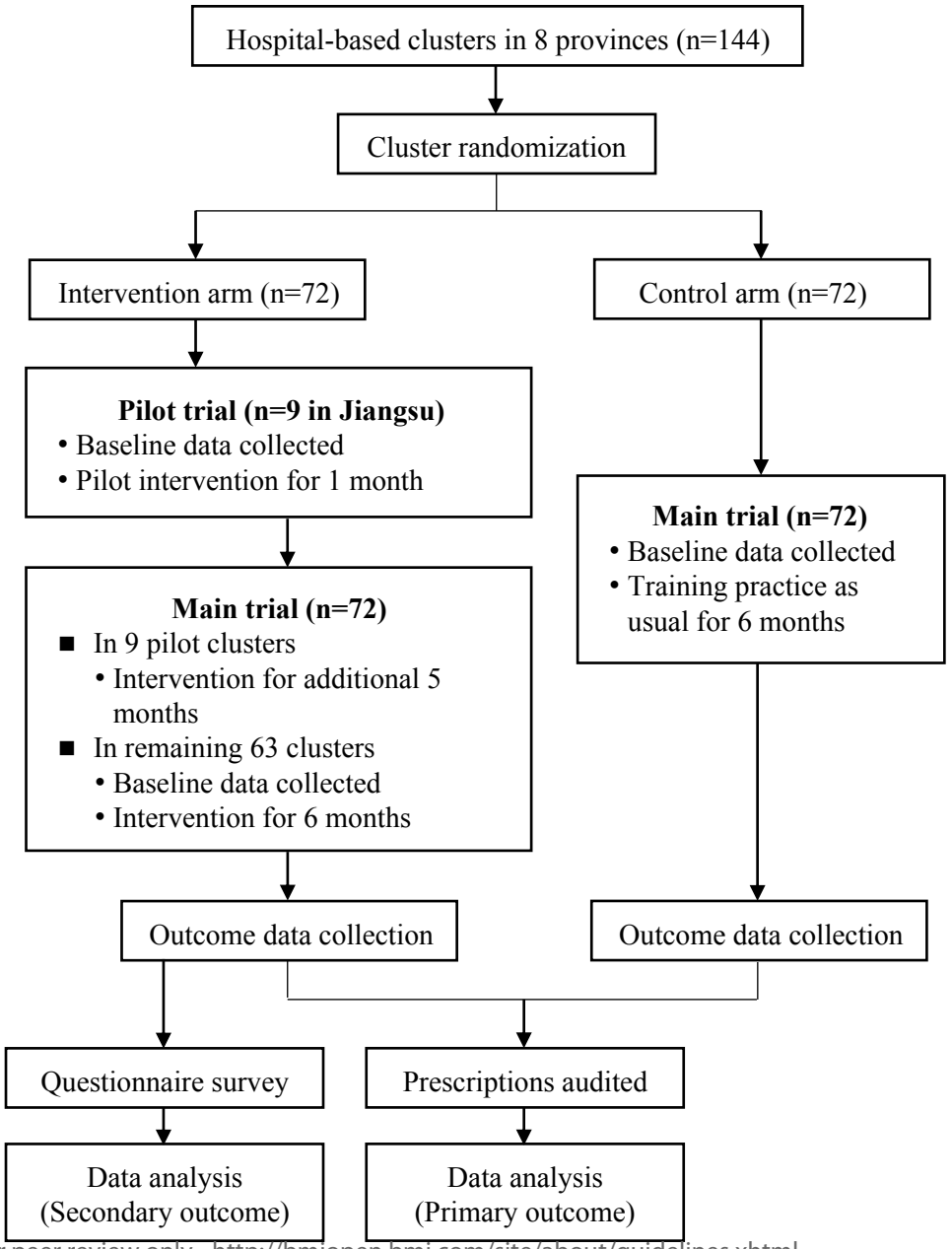
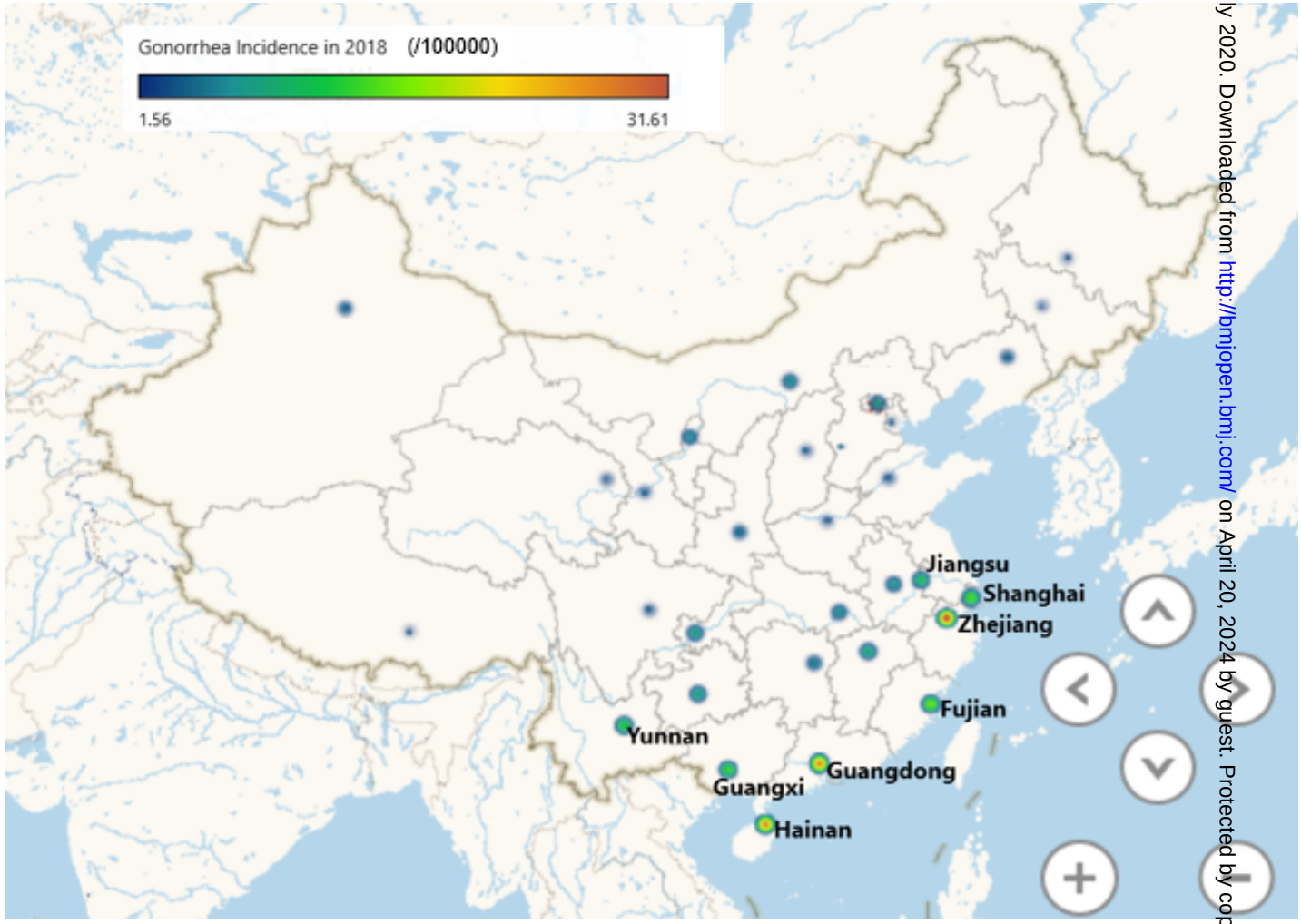
Figure 1. Flow chart of the prospective cluster randomized trial.

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

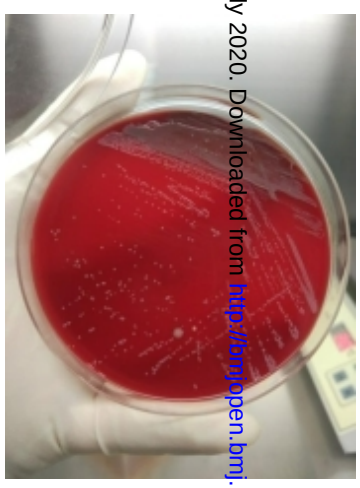
Figure 3. The information card with a QR code (hosted by WenJuanXing) to be distributed to physicians in the intervention hospitals.





Gonorrhea

- Class B notifiable infectious disease ;
- Infectious disease caused by gonococcal infection ;
- Infectious disease resistant to a variety of antibiotics ;
- Infectious disease needed to be treated according to National Guidelines.



How to treat gonorrhea ?

National Center for STD Control, China CDC.

Venereology group in Dermatology and Venereology Branch of Chinese Medical Association.

Dermatology and Venereal disease prevention and control committee of Chinese Preventive Medical Association.

STD sub committee of Dermatologists Branch of Chinese Medical Doctor Association.

QR code

Please scan QR code @

Supplement 1. Hospital information

This form is used for collecting background information of the eligible hospitals for participating in the cluster randomized controlled trial. By providing this information, neither do you commit to participating in the trial nor is your hospital for sure allocated to a specific arm of the trial. It is guaranteed that confidentiality of this information can be ensured and the data from the information collection will be only used for anonymous analysis.
Thank you in advance for your time in providing this information.

Province: _____ **City:** _____ **Code:** _____ (*Assigned*)

Hospital name: _____

Hospital nature: ☐ General hospital; ☐ Specialized hospital; ☐ Community hospital;
☐ Other (Specific_____)

Hospital township: ☐ Public teaching hospital; ☐ Public non-teaching hospital;
☐ Private hospital; ☐ Other (Specific_____)

Hospital category: ☐ Primary hospital; ☐ Secondary hospital;
☐ Tertiary hospital; ☐ Uncategorized or others

Number of gonorrhea cases reported in the last year: _____

Department and staff: *Does the hospital have the following departments and how many doctors qualified are there in each department for managing patients with sexually transmitted infections?*

☐ Dermatology (dermatovenerology); Number of doctors: _____
☐ Urology; Number of doctors: _____
☐ Andrology; Number of doctors: _____

Availability of antibiotics: *Does this hospital stock the following antibiotics and what are their dosage forms?*

Ceftriaxone (injectable): ☐ 250mg; ☐ 500mg; ☐ 1g;
☐ 2g; ☐ Other (Specific: _____)

Spectinomycin (injectable): ☐ 2g; ☐ Other (Specific: _____)

Does the hospital agree to participate in the study? ☐ Yes; ☐ No

Supplement 2. Questionnaire survey for the physicians in the participating hospitals

This form is used for collecting socio-demographic information anonymously. You are invited to participate in this questionnaire survey which takes you about less than 5 minutes to answer all questions. By completing this questionnaire, you are not automatically required to commit to participating in the intervention trial later on. Participation in this survey is totally voluntary and you can choose either participation to answer all or some questions or rejection to participate. Any choice does not influence the relationship between you and the investigators.
Thank you in advance for your time in completing this questionnaire.

1. Your gender:

- ❍ Male
- ❍ Female

2. Your age:

- ❍ <25
- ❍ 25~35
- ❍ 35~45
- ❍ 45~55
- ❍ 55~65
- ❍ >65

3. What is the highest degree that you have obtained?

- ❍ Post-Doctor
- ❍ Doctor
- ❍ Master
- ❍ Bachelor
- ❍ Other (Specific: _____)

4. The name of hospital you are working at:

- ❍ _____ (Text)

5. What department do you work in the hospital?

- ❍ Dermatology & STD
- ❍ Andrology
- ❍ Urology department
- ❍ Obstetrics and gynecology
- ❍ Other (Specific: _____)

6. **How long have you been working in this department?**

- ❍ ≤5 years
- ❍ 6~10 years
- ❍ ≥11 years

7. Your professional title is:

- ❍ Chief physician
- ❍ Associate chief physician
- ❍ Physician-in-charge
- ❍ Resident physician
- ❍ Other (Specific: _____)

8. In the last three months, approximately how many cases of uncomplicated gonorrhea have you treated?

- ❍ _____ (Number)

Supplement 3. Baseline data on prescriptions

This form is used for retrospectively collecting data derived from the most recent 30 prescriptions PRIOR to the trial in each of departments in each of participating hospitals. It is guaranteed that confidentiality of these data can be ensured, and these data will be only used for anonymous analysis.
Thank you in advance for your time in providing these data.

Province: _____ **City:** _____ **Code:** _____ (*Assigned*)

Hospital name: _____

Department: ☐ Dermatology (dermatovenerology)
☐ Urology
☐ Andrology

Prescription information

Number	Patient's gender	Patient's age	Diagnosis	Treatment		
				Drug	Dosage	Duration

Supplement 4. Endline data on prescriptions

This form is used for collecting data derived from the most recent prescriptions of each department in each of participating hospitals AFTER the trial. It is guaranteed that confidentiality of these data can be ensured, and these data will be only used for anonymous analysis. Thank you in advance for your time in providing these data.

Province: _____ **City:** _____ **Code:** _____ (*Assigned*)

Hospital name: _____

Department: ☐ Dermatology (dermatovenerology)
☐ Urology
☐ Andrology

Prescription information

Number	Patient's gender	Patient's age	Diagnosis	Treatment		
				Drug	Dosage	Duration

Supplement 5. Questionnaire survey for the physicians in the intervention hospitals

This form is used for collecting information anonymously after a cluster randomized controlled trials (RCT) is conducted at your hospital. You are invited to participate in this questionnaire survey which takes you about 10 minutes to answer all questions. Participation in this survey is totally voluntary and you can choose either participation to answer all or some questions or rejection to participate. Any choice does not influence the relationship between you and the investigators.

Thank you in advance for your time in considering this questionnaire survey or completing this questionnaire.

1. Your gender:

- ❍ Male
- ❍ Female

2. Your age:

- ❍ <25
- ❍ 25~35
- ❍ 35~45
- ❍ 45~55
- ❍ 55~65
- ❍ >65

3. What is the highest education degree that you have obtained?

- ❍ Post-Doctor
- ❍ Doctor
- ❍ Master
- ❍ Bachelor
- ❍ Other (Specific: _____)

4. The name of hospital you are working at:

- ❍ _____ (Text)

5. What department do you work in the hospital?

- ❍ Dermatology & STD
- ❍ Andrology
- ❍ Urology department
- ❍ Obstetrics and gynecology
- ❍ Other (Specific: _____)

6. How long have you been working in this department?

- ❍ ≤5 years
- ❍ 6~10 years
- ❍ ≥11 years

7. Your current professional title is:

- ❍ Chief physician
- ❍ Associate chief physician
- ❍ Physician-in-charge
- ❍ Resident physician
- ❍ Other (Specific: _____)

8. In the last three months, approximately how many cases of uncomplicated gonorrhea have you treated?

- ❍ _____ (Number input) (If answer <1, Skip to End of Survey)

9. In the last three months, which antibiotic was your first choice for treatment of uncomplicated gonorrhea:

- ❍ Ceftriaxone (skip to 10)
- ❍ Spectinomycin (skip to 11)
- ❍ Cefotaxime (Skip to 12)
- ❍ Azithromycin (Skip to 12)
- ❍ Other (Specific: _____) (Skip to 12)

10. In the last three months, which dose of ceftriaxone did you prefer to use for treatment of uncomplicated gonorrhea:

- ❍ 0.25g
- ❍ 0.5g
- ❍ 1.0g
- ❍ >=2.0g

11. Why do you prefer to prescribe spectinomycin for treatment of uncomplicated gonorrhea?

- ❍ More effective
- ❍ More convenient
- ❍ Our clinic could not provide cephalosporin
- ❍ Other (Specific: _____)
- ❍ No applicable as I did not refer to prescribe spectinomycin

12. Before participating in the on-line video-based training, do you know about the up-to-dated National STD Treatment Guidelines for treatment of uncomplicated gonorrhea (ceftriaxone 500 mg, or spectinomycin 2 or 4 g IM as a single dose)?

- ❍ Yes
- ❍ No

13. In the last six months, how many times did you access to the on-line training video developed on the WenJuanXing platform?

- ❍ 0
- ❍ 1~3
- ❍ 4~6
- ❍ ≥7

14. In the last six months, have you received other relevant trainings on treatment of gonorrhea?

- ❍ Yes (Specific: _____)
- ❍ No

15. What do you think about the up-to-dated regimen in the National STD Treatment Guidelines for treatment of uncomplicated gonorrhea using ceftriaxone 500 mg as a single dose?

- ❍ Appropriate (enough) dosage
- ❍ Dosage is overdose
- ❍ Dosage is not enough
- ❍ Difference from case to case
- ❍ Don't know

16. Do you think this on-line video-based training programme is helpful for improving your knowledge on management of gonorrhea?

- ❍ Very helpful
- ❍ Helpful
- ❍ Not helpful
- ❍ Don't know

17. Do you think the participation in this on-line video-based training programme every two months occupy too much of your time?

- ❍ Yes
- ❍ No

18. Will you continue to use this on-line video-based training programme?

- ❍ Yes
- ❍ No

19. Are you willing to recommend this on-line video-based training programme to other colleagues?

- ❍ Yes
- ❍ No

20. Do you have any suggestions on the on-line training programmes?

- ❍ Yes (Specific: _____)
- ❍ No

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

Section/item	ItemNo	Description	Addressed on page number
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	Chinese Clinical Trial Registry (ChiCTR)
	2b	All items from the World Health Organization Trial Registration Data Set	Chinese Clinical Trial Registry (ChiCTR)
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	11
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	1
	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	12

	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)	6
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	5-6
	6b	Explanation for choice of comparators	6
Objectives	7	Specific objectives or hypotheses	6
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)	8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8

	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)	6
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	8
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
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	9
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)	Figure 1
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	7
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7

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	8
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	8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
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	9-10
	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	8

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	11
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	10
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	10
	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)	10
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	11
	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	10
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	6
Ethics and dissemination			

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	11
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)	11
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	11
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	11
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	11
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	12
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	11
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	11
	31b	Authorship eligibility guidelines and any intended use of professional writers	11

	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	11
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Figure 3
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	N/A

*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.

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A novel education-based intervention to reduce inappropriate antibiotic prescribing for treatment of gonorrhea in China: protocol for a cluster randomized controlled trial

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ABSTRACT

Introduction: Inappropriate use of antibiotics in treatment of gonorrhea in clinical practice may facilitate emergence of gonococcal antimicrobial resistance. Education programme may be helpful for improving physicians' prescribing behaviors to follow the treatment guidelines. As traditional education based on printed materials may have limited effect on the compliance, innovative education strategies are needed. The trial is aimed to assess a novel education intervention in improving compliance with the national guidelines in antibiotic prescribing for treatment of gonorrhea in China.

Methods and analysis: We will conduct a cluster randomized control trial (cluster-RCT) across 144 hospitals (clusters) in 8 provinces in China. The intervention procedures will include to introduce an on-line training video on WenJuanXing platform to all physicians who work in the out-patient departments of dermatology (dermatovenerology), urology, andrology or gynaecology. By scanning QR code, physicians could access to the training video. The video covers workflows and requirements for managing a patient with uncomplicated gonorrhea, and provides the contact information for inquiring any questions as well. In hospitals allocated to the control arm, physicians will continue to participate in their training programme if they conventionally do it. The primary outcome is to estimate the proportion of prescriptions adherent to the regimens (1g intramuscular ceftriaxone single dose) recommended by the National Guidelines for treatment of uncomplicated gonorrhea at the cluster level. In addition, to understand physician's barriers 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) and all physicians will provide an informed consent prior to participation in the surveys. The findings of the trial will be disseminated through conferences, peer-reviewed journals, and developing training programmes for physicians.

Keywords: gonorrhea, antibiotic, prescribing behavior, education, cluster randomized controlled trial

Strengths and limitations of this study

- The study design (cluster randomized controlled trial, cluster-RCT) is a robust methodology to assess the effectiveness of behavioral interventions.
- The study will be carried out in 8 different provinces, providing potentially useful information about the extent to which implementation of the intervention is likely to be influenced by local context.
- Questionnaire survey on physicians before initiating the intervention may influence the prescribing behaviors of physicians from control hospitals, which underestimates the effect of intervention.

Trial registration number ChiCTR2000029591.

INTRODUCTION

Gonorrhea, caused by *Neisseria gonorrhoeae* (*N. gonorrhoeae*), remains one of the most common sexually transmitted diseases (STDs) worldwide. According to the most recent World Health Organization (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 behavioral interventions to prevent becoming infected with this disease, timely detection of the infection followed by effective treatment with antibiotics remain the mainstream strategy for control of 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 gonorrhea 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] and treatment failures with ceftriaxone have been reported in Japan, Australia, European countries, Canada, and South Africa.[10-13] The data from the China Gonococcal Resistance Surveillance Programme (China-GRSP) 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 recognized that much of the antimicrobial resistance (AMR) of gonorrhea 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 gonorrhea 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 gonorrhea 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 1g for their treatment.[17] Several factors affect physicians' prescribing behaviors, 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 gonorrhea among physicians who were aware of the guidelines than those who were not but the participation in training courses did not significantly improve the prescribing behaviors,[18] indicating that more innovative interventions are needed to address the issues of inappropriate antibiotic use in treatment of gonorrhea in China. To explore the innovative strategies to ensure appropriate use of antibiotics for treatment of gonorrhea has been listed as one of priorities in a comprehensive research plan called the 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 randomized controlled trials (RCTs) in some medical fields have revealed the success of mHealth in optimizing antibiotic prescribing.[22-24] However, there are no studies that shed light on whether such training programme is beneficial to improving antibiotic prescribing behaviors among physicians who provide treatment to patients with STDs. For this purpose, we will conduct a prospective cluster randomized trial with a primary objective to observe whether the proposed intervention (on-line video-based training programme) could significantly improve physicians' prescribing behaviors to adhere to the up-to-dated National Guidelines[25] in treatment of uncomplicated gonorrhea (1g intramuscular ceftriaxone single dose). Our secondary objective is to understand physicians' barriers to the on-line video-based training programme.

METHODS AND ANALYSIS

Study design and setting

The proposed study will use a cluster-randomized controlled trial design, consisting of two arms (**Figure 1**), to evaluate whether our intervention improves the physicians' adherence to the National Guidelines in antibiotic prescribing for treatment of uncomplicated gonorrhea.

Selection of provinces for the study is based on the reported incidence of gonorrhea in 2018. The 8 provinces (Jiangsu, Shanghai, Zhejiang, Fujian, Guangdong, Guangxi, Hainan and Yunnan) are purposively selected from 31 provinces in mainland China in consideration of their higher incidence of reported gonorrhea cases than the national average (**Figure 2**).

Within each study province, we will invite the city-level hospitals with the high volume of reported gonorrhea cases to participate in the study. The hospitals at national or province-level in the study provinces will be excluded because small number of such hospitals within a province makes a difficulty to ensure comparable assignments of these hospitals into intervention and control arms. Hospitals will be used for randomization of them into intervention or control arm, with randomization stratified by province considering the potential for important variation in outcomes between the provinces. Core elements of the intervention are on-line training on antibiotic prescribing for treatment of uncomplicated gonorrhea 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 sub-trials, i.e., pilot and main trials. The internal pilot trial will be conducted in one province randomly selected from the 8 study provinces to collect the data simultaneously in 9 intervention and 9 control hospitals during a period of one month for examining feasibility and acceptability of the intervention. If more than 60% of physicians are willing to accept the intervention, the internal pilot hospitals and their outcome data will then become part of the main trial, and will be followed up for a further 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, programme manager, hospital representatives and statistician will be established to oversee the trail 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 July 2021. The hospital selection and project coordinator recruitment will take place in October 2020. Baseline assessments will be carried out before randomization 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 high volume of reported gonorrhea cases are eligible for participating in the study. Our investigators will prepare a list of eligible hospitals in each of the 8 study provinces. These hospitals will be invited to participate in the study by explaining the objectives and processes of the study to the hospitals' administrators and the in-hospital project coordinators. If the hospital agree 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 out-patient departments of dermatology (dermatovenerology), urology, andrology or gynaecology and provide informed consent (**see Supplement 1**) will be eligible for participating in the study. Prescriptions of these physicians for treatment of uncomplicated gonorrhea will be eligible for evaluating the adherence to the National Guidelines, but prescriptions will be excluded from data analysis if they are prescribed to the patients who meet any of the following criteria: (1) being 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) being diagnosed as complicated gonorrhea, such as disseminated gonococcal infection and pelvic inflammatory disease (PID).

Intervention and control

The proposed intervention to be validated 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 QR code on the information card (**Figure 3**), physicians could access to an on-line 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 gonorrhea, including diagnostic criteria and treatment recommendations in accordance with the National Guidelines, and provides the contact infection for enquiring any questions related to the diagnosis and treatment as well.

In the intervention arm hospitals, project coordinators will provide a less than 30-minutes interactive training session in each of the relevant departments (integrated within monthly department meeting) prior to implementation of the intervention to interpret the information card and the way to use the QR code for accessing to the on-line training video. The intervention of video-based training will last for 6 months and during the 6 months the participating physicians will be reminded for video playback by the project coordinators through sending a WeChat message monthly.

The visiting frequency of the on-line 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 gonorrhea cases according to their own knowledge and believes.

Outcomes

The primary outcome is the proportion of prescriptions adherent to the regimens for treatment of uncomplicated gonorrhea recommended by the National Guidelines at the cluster level. The most recent 100 eligible prescriptions will be obtained by the prescription assessors from each study hospital prior to implementation of the intervention as baseline data and 6 months after the implementation for evaluating the outcome.

The secondary outcome is to understand physician's barriers to the on-line video-based training programme, including physician's socio-demographic characteristics, education background, working experience, and those relating to physicians' perceptions, attitudes, and practices.

Sample size estimation

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

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

where $Z_{\alpha/2}$ is the critical value of the normal distribution at $\alpha/2$ (for a confidence level of 95%, α is 0.05 and the critical value is 1.96), Z_{β} is the critical value of the normal distribution at β (for a power of 90%, β is 0.1 and the critical value is 1.28); π_0 and π_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_{β} = 1.28, π_0 = 37.8% (based on a nationwide survey[18] in China), π_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 gonorrhea patients per hospital within six 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% loss of data and a necessity to do stratified randomization, a total of 144 hospitals will be recruited in the 8 provinces for the study (18 hospitals in each province).

Cluster randomization

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 hospital from other cities will be purposively selected in consideration of a high volume of reported cases. In each stratification, a simple randomization process will be used to assign the hospitals into intervention or 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 one of the 8 provinces participating in our study. After all 144 hospitals were randomized, one province will be randomly selected from the 8 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 (9 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**). Randomization is conducted by independent statistical analysts using a computer program written in R (V.3.5.3).

The trial will be not possible to blind either in-hospital project coordinators or participating physicians on the arm assignment, given the explicit nature of the intervention components (e.g. physicians in the intervention hospitals will be trained by in-hospital project

coordinators). However, the prescription assessors and 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

Physicians' names will never appear in any datasets of the study but the physician who participates in the study will be assigned a 4-digit working number by the project coordinators and use this number as a study code in the questionnaire surveys and prescription audits. This number will be only known by the project coordinator and 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 Supplement 2**) and another baseline questionnaire survey to collect background information of the participating physicians (**see Supplement 3**) in both intervention and control groups for evaluating the appropriateness of randomization. A specific questionnaire survey (**see Supplement 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 (HIS), 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, diagnoses and medications, as well as linked prescribing physician's name, using a data collection form (**see Supplement 5 and Supplement 6**).

Data analysis

The data analysis are described in full detail in the accompanying data collection and analysis plan (**see Supplement 7**) and are, therefore, only outlined in brief here. We will conduct 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 analyses 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 summarized 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 analyses 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% confidence interval 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 analyses, considering adjusting increases power and reduces the effect of imbalances between arms with typically minimal risks. We will also conduct a subgroup analyses on primary outcome to indicate the intervention effect across the subgroups in terms of hospitals and physicians. For the secondary outcome, we will define the physician who have at least 25% prescriptions nonadherent to the National Guidelines as the physicians with nonadherence, and then use multivariate logistic regression model to identify the independent variables associated with the nonadherence at a significant level of $p \leqslant 0.05$ and estimate adjusted odds ratio (AOR) 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 for conducting 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 analyzed 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 involved during the conduct of the study by giving feedback on their barriers to comply with the intervention during the pilot trial in order to tailor 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 authorized individuals for data analysis and reporting purposes only. Data will be entered into the database in an anonymized form to ensure confidentiality. Only principal investigator and other authorized 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, publishing at least two papers in the peer-reviewed journals, and provision of evidence for developing the on-the-job training programmes for physicians who provide services to patients with STD.

Contributors

XSC: conceptualized the study. TTJ, YQY and XSC: designed the study. NXC and YPY: participated in the study design. TTJ: wrote the first draft of this protocol. XSC: made critical revision of the study protocol. YQY, NXC and YPY: contributed to the revision of the study protocol. All authors reviewed and approved the final manuscript.

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Disclaimer

The funders of the study had no role in the design of the trial, and writing of the study protocol, and decision on submission of the manuscript for publication.

Competing interests

None declared.

Patient consent

Not required.

Ethics approval

Ethical approval for this study was obtained from the Chinese Academy of Medical Sciences Institute of Dermatology in Nanjing (2020-LS-004).

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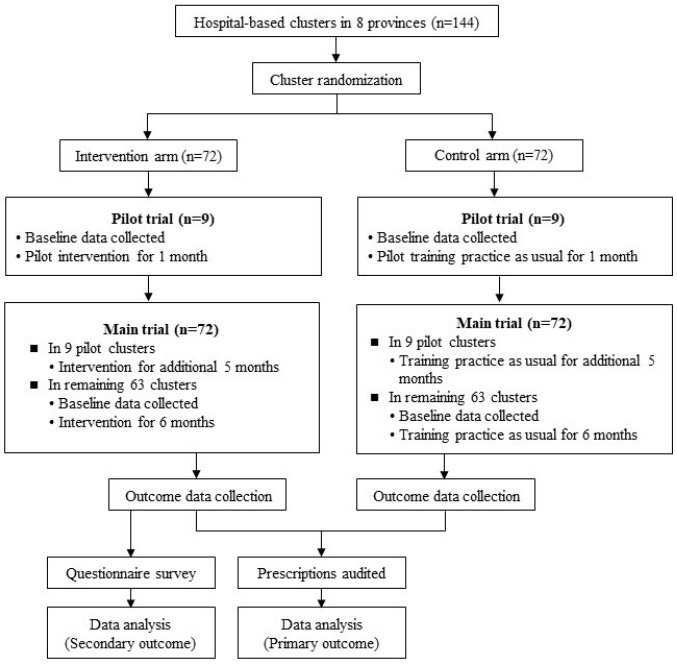
Figure Legends

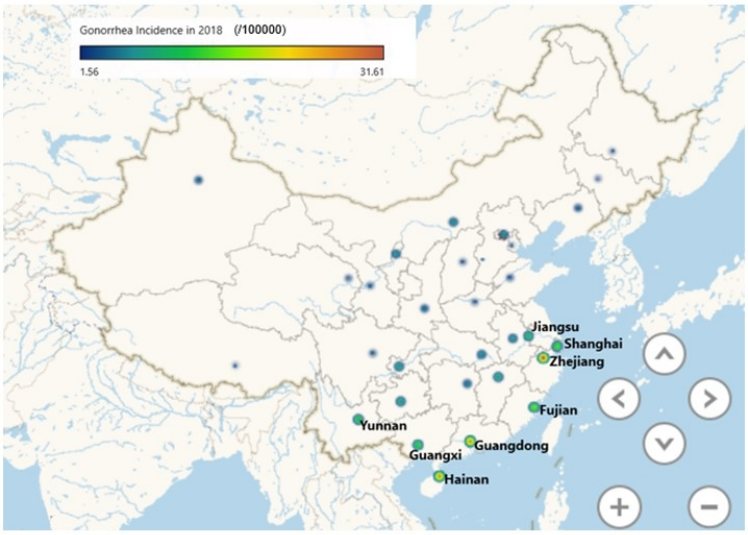
Figure 1. Flow chart of the prospective cluster randomized trial.

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

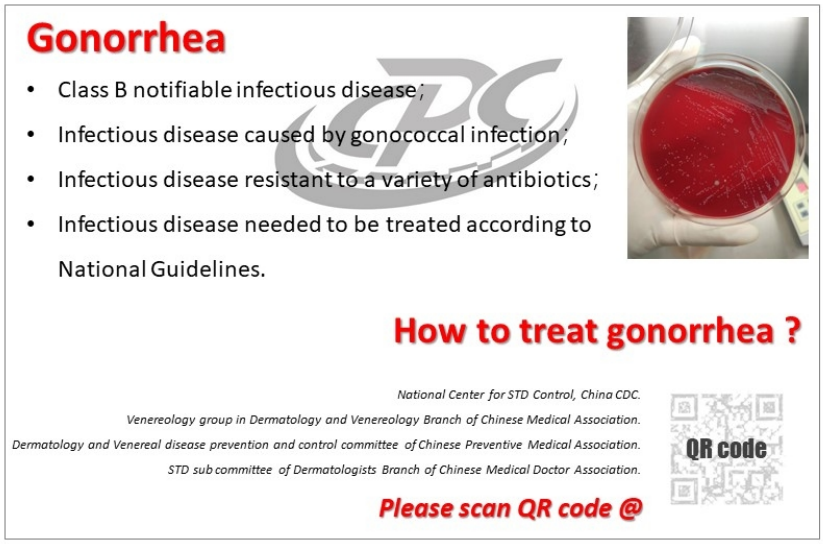
Figure 3. The information card with a QR code (hosted by WenJuanXing) to be distributed to physicians in the intervention arm hospitals.



254x190mm (96 x 96 DPI)



254x190mm (96 x 96 DPI)



254x190mm (96 x 96 DPI)

Supplement 1. Participant informed consent form

About this Study

You are being asked to take part in a research study that will help us better understand prescribing behavior for treatment of uncomplicated gonorrhea among physicians in China. Your participation in this project will allow us to develop better interventions to improve physicians' prescribing behaviors to follow the treatment guidelines.

What's involved?

Our study participants consist of physicians from eight provinces including Jiangsu, Shanghai, Zhejiang, Fujian, Guangdong, Guangxi, Hainan, and Yunnan. If you participate in this study, you will be asked to complete an online questionnaire. A subset of participants will be asked to complete an additional follow-up questionnaire. The questionnaires will ask you to provide sociodemographic information and information about your comment on the interventions we provided. In addition, your prescriptions for uncomplicated gonorrhea will be randomly selected and audited. In order to ensure that your privacy is protected, all of your online responses will be encrypted and securely transferred to our data servers.

Voluntary participation

A decision not to participate or to withdraw from participation will not affect your relationship with the hospital in any way.

Discomfort and risks

Our study does not introduce any additional risk or discomfort to participants.

Compensation

No financial incentives are offered for participating in the study.

Questions

All research on human volunteers is reviewed by a committee that works to protect your rights and welfare. If you have any questions about the research or your participation in the study, feel free to contact Ting-Ting Jiang (021-85478901).

Participant statement

○ I have been informed about this study and understand what is involved. I also know whom to contact if I need more information. I understand that confidentiality will be preserved. I agree to participate in this study.

Supplement 2. Hospital information

This form is used for collecting background information of the eligible hospitals for participating in the cluster randomized controlled trial. By providing this information, neither do you commit to participating in the trial nor is your hospital for sure allocated to a specific arm of the trial. It is guaranteed that confidentiality of this information can be ensured and the data from the information collection will be only used for anonymous analysis.
Thank you in advance for your time in providing this information.

Province: _____ **City:** _____ **Code:** _____ (*Assigned*)

Hospital name: _____

Hospital nature: ☐ General hospital; ☐ Specialized hospital; ☐ Community hospital; ☐ Other (Specific_____)

Hospital township: ☐ Public teaching hospital; ☐ Public non-teaching hospital; ☐ Private hospital; ☐ Other (Specific_____)

Hospital category: ☐ Primary hospital; ☐ Secondary hospital; ☐ Tertiary hospital; ☐ Uncategorized or others

Number of gonorrhea cases reported in the last year: _____

Department and staff: *Does the hospital have the following departments and how many doctors qualified are there in each department for managing patients with sexually transmitted infections?*

☐ Dermatology (dermatovenerology); Number of doctors: _____
☐ Urology; Number of doctors: _____
☐ Andrology; Number of doctors: _____
☐ Gynaecology; Number of doctors: _____

Availability of antibiotics: *Does this hospital stock the following antibiotics and what are their dosage forms?*

Ceftriaxone (injectable): ☐ 250mg; ☐ 500mg; ☐ 1g; ☐ 2g; ☐ Other (Specific: _____)
Spectinomycin (injectable): ☐ 2g; ☐ Other (Specific: _____)

Does the hospital agree to participate in the study? ☐ Yes; ☐ No

Supplement 3. Questionnaire survey for the physicians in the participating hospitals

This form is used for collecting socio-demographic information. You are invited to participate in this questionnaire survey which takes you about less than 5 minutes to answer all questions. By completing this questionnaire, you are not automatically required to commit to participating in the intervention trial later on. Participation in this survey is totally voluntary and you can choose either participation to answer all or some questions or rejection to participate. Any choice does not influence the relationship between you and the investigators.

Thank you in advance for your time in completing this questionnaire.

1. Your working number:

❍ □□□□ (*Assigned*)

2. Your gender:

❍ Male

❍ Female

3. Your age:

❍ <25

❍ 25~35

❍ 35~45

❍ 45~55

❍ 55~65

❍ >65

4. What is the highest degree that you have obtained?

❍ Post-Doctor

❍ Doctor

❍ Master

❍ Bachelor

❍ Other (Specific: _____)

5. What department are you working?

- ❍ Dermatology & STD
- ❍ Andrology
- ❍ Urology department
- ❍ Obstetrics and gynecology
- ❍ Other (Specific: _____)

7. How long have you been working in this department?

- ❍ ⩽5 years
- ❍ 6~10 years
- ❍ ⩾11 years

8. Your professional title is:

- ❍ Chief physician
- ❍ Associate chief physician
- ❍ Physician-in-charge
- ❍ Resident physician
- ❍ Other (Specific: _____)

9. In the last three months, approximately how many cases of uncomplicated gonorrhea have you treated?

- ❍ □□□□ (Number)

10. In the last three months, have you received relevant trainings on treatment of gonorrhea?

- ❍ Yes (Specific: _____)
- ❍ No

Supplement 4. Questionnaire survey for the physicians in the intervention hospitals

This form is used for collecting information after a cluster randomized controlled trials (RCT) is conducted at your hospital. You are invited to participate in this questionnaire survey which takes you about 10 minutes to answer all questions. Participation in this survey is totally voluntary and you can choose either participation to answer all or some questions or rejection to participate. Any choice does not influence the relationship between you and the investigators.

Thank you in advance for your time in considering this questionnaire survey or completing this questionnaire.

1. Your working number:

❍ □□□□ (*Assigned*)

2. Your gender:

❍ Male

❍ Female

3. Your age:

❍ <25

❍ 25~35

❍ 35~45

❍ 45~55

❍ 55~65

❍ >65

4. What is the highest education degree that you have obtained?

❍ Post-Doctor

❍ Doctor

❍ Master

❍ Bachelor

❍ Other (Specific: _____)

5. The name of hospital you are working at:

- ❍ _____ (Text)

6. What department do you work in the hospital?

- ❍ Dermatology & STD
- ❍ Andrology
- ❍ Urology department
- ❍ Obstetrics and gynecology
- ❍ Other (Specific: _____)

7. How long have you been working in this department?

- ❍ ≤5 years
- ❍ 6~10 years
- ❍ ≥11 years

8. Your current professional title is:

- ❍ Chief physician
- ❍ Associate chief physician
- ❍ Physician-in-charge
- ❍ Resident physician
- ❍ Other (Specific: _____)

9. In the last three months, approximately how many cases of uncomplicated gonorrhea have you treated?

- ❍ _____ (Number input) (If answer <1, Skip to End of Survey)

10. Before participating in the on-line video-based training, do you know about the up-to-dated National STD Treatment Guidelines for treatment of uncomplicated gonorrhea?

- ❍ Yes
- ❍ No

11. In the last six months, how many times did you access to the on-line training video developed on the WenJuanXing platform?

- ❍ 0
- ❍ 1~3
- ❍ 4~6
- ❍ ≥7

12. In the last six months, have you received other relevant trainings on treatment of gonorrhea?

- ❍ Yes (Specific: _____)
- ❍ No

13. What do you think about the up-to-dated regimen in the National STD Treatment Guidelines for treatment of uncomplicated gonorrhea using ceftriaxone 1g as a single dose?

- ❍ Appropriate (enough) dosage
- ❍ Dosage is overdose
- ❍ Dosage is not enough
- ❍ Difference from case to case
- ❍ Don't know

14. Do you think this on-line video-based training programme is helpful for improving your knowledge on management of gonorrhea?

- ❍ Very helpful
- ❍ Helpful
- ❍ Not helpful
- ❍ Don't know

15. Do you think the participation in this on-line video-based training programme every two months occupy too much of your time?

- ❍ Yes
- ❍ No

16. Will you continue to use this on-line video-based training programme?

- ❍ Yes
- ❍ No

17. Are you willing to recommend this on-line video-based training programme to other colleagues?

- ❍ Yes
- ❍ No

18. Do you have any suggestions on the on-line training programmes?

- ❍ Yes (Specific: _____)
- ❍ No

Supplement 5. Baseline data on prescriptions

This form is used for retrospectively collecting data derived from the eligible prescriptions PRIOR to the trial in each of departments in each of participating hospitals. It is guaranteed that confidentiality of these data can be ensured, and these data will be only used for anonymous analysis.

Thank you in advance for your time in providing these data.

Province: _____ **City:** _____ **Code:** _____ (*Assigned*)

Hospital name: _____

Department:

☐ Dermatology (dermatovenerology)

☐ Urology

☐ Andrology

☐ Gynaecology

Prescription information

No.	Patient' gender	Patient's age	Diagnosis	Treatment			Physician's working number
				Drug	Dosage	Duration	
							☐☐☐☐
							☐☐☐☐
							☐☐☐☐
							☐☐☐☐
							☐☐☐☐
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							☐☐☐☐
							☐☐☐☐

Supplement 6. Endline data on prescriptions

This form is used for collecting data derived from the eligible prescriptions AFTER the trial in each of department in each of participating hospitals. It is guaranteed that confidentiality of these data can be ensured, and these data will be only used for anonymous analysis.
Thank you in advance for your time in providing these data.

Province: _____ **City:** _____ **Code:** _____ (*Assigned*)

Hospital name: _____

Department:
☐ Dermatology (dermatovenerology)
☐ Urology
☐ Andrology
☐ Gynaecology

Prescription information

No.	Patient' gender	Patient's age	Diagnosis	Treatment			Physician's working number
				Drug	Dosage	Duration	
							☐☐☐☐
							☐☐☐☐
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Supplement 7. Data Collection and analysis plans prior to implementing the prospective cluster randomized controlled trial

The analyses presented in the current manuscript evolved from the following research question and associated data collection and analysis:

1. **How will we evaluate the appropriateness of randomization?**
   a) We will use questionnaires to collect the background information of participating hospitals (hospital's level, and category) and participating physicians (sex, age, education level, working year, department, and previous training).
   b) We will estimate the differences between the intervention and control arms in cluster (hospital)'s characteristics including level (capital vs. other city), and category (general vs. specialized hospital).
   c) We will compare the differences between the intervention and control arms in participating physician's characteristics including sex, age, education level, working year, department, and previous training.
2. **How will we evaluate the missing data?**
   a) We will define the physicians who provide informed consent and are willing to participate in the study and then withdraw from the intervention or are unwilling to have their prescriptions audited later on as missing participants.
   b) We will identify the missing participants from the complete dataset and define the data of these participants as missing data.
   c) We will compare the differences between the missing data and the data for analysis in participating physician's characteristics including sex, age, education level, working year, department, and previous training.
3. **What are the determinants used to describe the adherence rate to the National Guidelines and intervention effect for measuring the primary outcome?**
   a) We will collect the most recent 100 eligible prescriptions from each participating hospital (cluster) prior to intervention implementation period and 6 months after the implementation.

b) We will define the regimen of 1 g ceftriaxone described by the participating physician for treatment of uncomplicated gonorrhea as adherence to the National Guidelines (dichotomous outcome).

c) We will estimate the adherence rate and its 95% confidence intervals (CIs) using the total number of eligible prescriptions and the number of the prescriptions met the criteria of adherence.

d) We will estimate the intervention effect which is reported as rate ratio (RR) and 95% CIs compared with the control group. The stratum-specific endline adherence rate ratios will be calculated from the stratum-specific endline adherence rates (mean cluster-level outcomes) in each arm. The crude intervention effect as the overall endline adherence rate ratio between the intervention arm and control arm will be estimated from the weighted average of the stratum-specific endline adherence rate ratios, with weights that are inversely proportional to the stratum-specific variances. Formal testing of the null hypothesis that the overall adherence rate ratio is equal to 1 will be conducted using stratified t-test, and 95% confidence interval will be adjusted for between-cluster variance and stratification. To adjust for potentially important covariates, including cluster-level outcome at baseline, and additional patient (age [years], sex [male, female]), linked physician (age [years], sex [male, female], education level [bachelor degree or higher, other], working year [years], department [dermatology or dermatovenerology, other], previous training [yes, no]) and hospital (province located) factors, a two-stage adjusted analyses will be conducted. 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 individual-level model predicted values and the individual-level observed values will be used to calculate covariate-adjusted cluster-level ratio residuals. The covariate-adjusted ratio residuals will then be used in place of cluster specific proportions to conduct stratified t-test and calculate 95% confidence interval 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 analyses, considering adjusting increases power and reduces the effect of imbalances between arms with typically minimal risks.

e) We will calculate the differences over 6 months of the intervention in both intervention and control groups, respectively.

f) We will also conduct subgroup analyses on primary outcome to indicate the intervention effect across the subgroups in terms of hospitals [hospital's level, and category] and physicians [sex, age, education level, working year, department, and previous training]. The same main analysis approach planned above will be used for the cluster-level subgroup analyses to obtain estimates of the treatment effect, its 95% confidence interval and statistical significance within each subgroup. To estimate the statistical significance of any differences in treatment effect among subgroups, analysis of variance will be used on the cluster-level summary outcome data, with terms for treatment, subgroup and the interaction between treatment and subgroup.

4. How will we measure the barriers to non-adherence to the National Guidelines for measuring the secondary outcome?

a) We will collect the physician's information on socio-demographic characteristics, education background, working experience, and perceptions, attitudes, and practices using a questionnaire survey in the intervention hospitals.

b) We will define the physician who have at least 25% prescriptions nonadherent to the National Guidelines as the physicians with nonadherence.

c) We will use the nonadherence as dependent variables for the analyses to identify the factors influencing the nonadherence.

d) We will use bivariate analyses to test associations between each of independent variables (socio-demographic characteristics, education background, working experience, and perceptions, attitudes, and practices) and the nonadherence (dependent variable). Independent variables with significance level of $p<0.10$ will be included in multivariate logistic regression model.

e) We will use multivariate logistic regression model to identify the independent variables associated with the nonadherence at a significant level of $p\leq0.05$ and estimate adjusted odds ratio (AOR) and its 95% CIs by adjusting for potential confounding factors.

TIDieR
Template for Intervention Description and Replication

The TIDieR (Template for Intervention Description and Replication) Checklist*:

Information to include when describing an intervention and the location of the information

Item number	Item	Where located **	
		Primary paper (page or appendix number)	Other † (details)
	BRIEF NAME		
1.	Provide the name or a phrase that describes the intervention.	Page 8	
	WHY		
2.	Describe any rationale, theory, or goal of the elements essential to the intervention.	Page 8	
	WHAT		
3.	Materials: Describe any physical or informational materials used in the intervention, including those provided to participants or used in intervention delivery or in training of intervention providers. Provide information on where the materials can be accessed (e.g. online appendix, URL).	Page 8	
4.	Procedures: Describe each of the procedures, activities, and/or processes used in the intervention, including any enabling or support activities.	Page 8-9	
	WHO PROVIDED		
5.	For each category of intervention provider (e.g. psychologist, nursing assistant), describe their expertise, background and any specific training given.	Page 8-9	
	HOW		

6.	Describe the modes of delivery (e.g. face-to-face or by some other mechanism, such as internet or telephone) of the intervention and whether it was provided individually or in a group.	Page 8-9	
	WHERE		
7.	Describe the type(s) of location(s) where the intervention occurred, including any necessary infrastructure or relevant features.	Page 8-9	
	WHEN and HOW MUCH		
8.	Describe the number of times the intervention was delivered and over what period of time including the number of sessions, their schedule, and their duration, intensity or dose.	Page 8-9	
	TAILORING		
9.	If the intervention was planned to be personalised, titrated or adapted, then describe what, why, when, and how.	N/A	
	MODIFICATIONS		
10.‡	If the intervention was modified during the course of the study, describe the changes (what, why, when, and how).	N/A	
	HOW WELL		
11.	Planned: If intervention adherence or fidelity was assessed, describe how and by whom, and if any strategies were used to maintain or improve fidelity, describe them.	Page 8-9	
12.‡	Actual: If intervention adherence or fidelity was assessed, describe the extent to which the intervention was delivered as planned.	N/A	

** **Authors** - use N/A if an item is not applicable for the intervention being described. **Reviewers** – use '?' if information about the element is not reported/not sufficiently reported.

† If the information is not provided in the primary paper, give details of where this information is available. This may include locations such as a published protocol or other published papers (provide citation details) or a website (provide the URL).

‡ If completing the TIDieR checklist for a protocol, these items are not relevant to the protocol and cannot be described until the study is complete.

* We strongly recommend using this checklist in conjunction with the TIDieR guide (see *BMJ* 2014;348:g1687) which contains an explanation and elaboration for each item.
* The focus of TIDieR is on reporting details of the intervention elements (and where relevant, comparison elements) of a study. Other elements and methodological features of studies are covered by other reporting statements and checklists and have not been duplicated as part of the TIDieR checklist. When a **randomised trial** is being reported, the TIDieR checklist should be used in conjunction with the CONSORT statement (see www.consort-statement.org) as an extension of **Item 5 of the CONSORT 2010 Statement.** When a **clinical trial protocol** is being reported, the TIDieR checklist should be used in conjunction with the SPIRIT statement as an extension of **Item 11 of the SPIRIT 2013 Statement** (see www.spirit-statement.org). For alternate study designs, TIDieR can be used in conjunction with the appropriate checklist for that study design (see www.equator-network.org).

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

Section/item	ItemNo	Description	Addressed on page number
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	ChiCTR2000029591
	2b	All items from the World Health Organization Trial Registration Data Set	ChiCTR2000029591
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	13
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	1
	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	13

	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)	7
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	5-6
	6b	Explanation for choice of comparators	6
Objectives	7	Specific objectives or hypotheses	6
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	8-9

	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)	8
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	8-9
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9
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	9
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)	7-8
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	9-10
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	10
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	10
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10
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	N/A
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	11
	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	11

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	13
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	11-12, Supplement 7
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	12
	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)	11
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	13
	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	12
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	7

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	12-13
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)	13
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
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	13
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
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	13
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	13
	31b	Authorship eligibility guidelines and any intended use of professional writers	13

	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	13
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplement 1
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	N/A

*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.

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A novel education-based intervention to reduce inappropriate antibiotic prescribing for treatment of gonorrhea in China: protocol for a cluster randomized controlled trial

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A novel education-based intervention to reduce inappropriate antibiotic prescribing for treatment of gonorrhea in China: protocol for a cluster randomized controlled trial

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ABSTRACT

Introduction: Inappropriate use of antibiotics to treat gonorrhea can lead to antibiotic resistance. Education programs may be helpful for improving physician prescribing behaviors 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 gonorrhea in China.

Methods and analysis: We will conduct a two-arm cluster randomized 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 gonorrhea. Outpatient physicians in dermatology (dermatovenerology), urology, andrology and gynaecology will be given access to the video via a QR 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 gonorrhea antibiotic prescriptions adherent to Chinese national guidelines at the cluster level. In addition, to understand the reasons of physician's nonadherence 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.

Keywords: gonorrhea, antibiotic, prescribing behavior, education, cluster randomized controlled trial

Strengths and limitations of this study

- The study design (cluster randomized controlled trial, cluster-RCT) is a robust methodology to assess the effectiveness of behavioral 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 behaviors of physicians from hospitals in the control arm, which may undermine the effect of intervention.

Trial registration number ChiCTR2000029591.

INTRODUCTION

Gonorrhea, caused by *Neisseria gonorrhoeae* (*N. gonorrhoeae*), remains one of the most common sexually transmitted diseases (STDs) worldwide. According to the most recent World Health Organization (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 behavioral interventions to prevent infection of gonorrhea, 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 gonorrhea 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 (China-GRSP) 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 recognized that much of the antimicrobial resistance (AMR) of gonorrhea 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 gonorrhea 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 gonorrhea 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 1g for their treatment.[17] Several factors affect physicians' prescribing behaviors, 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 gonorrhea among physicians who were aware of the guidelines than those who were not. Additionally, participation in training courses did not significantly improve the prescribing behaviors of physicians,[18] indicating that more innovative interventions are needed to address the issues of inappropriate antibiotic use in treatment of gonorrhea in China. Exploring innovative strategies to ensure appropriate use of antibiotics for treatment of gonorrhea 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 randomized controlled trials (RCTs) have shown success of mHealth in optimizing 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 behaviors among physicians who provide treatment to patients with STDs. For this purpose, we will conduct a cluster randomized trial to evaluate whether the proposed intervention (online video-based training programme) could significantly improve physicians' prescribing behaviors to adhere to the regimens for treatment of uncomplicated gonorrhea (1g 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' nonadherence to the online video-based training programme.

METHODS AND ANALYSIS

Study design and setting

We will use a parallel-group, cluster randomized controlled trial 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 gonorrhea in 2018. The eight provinces (Jiangsu, Shanghai, Zhejiang, Fujian, Guangdong, Guangxi, Hainan and Yunnan) with the highest incidence of reported gonorrhea 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 gonorrhea 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 randomized 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 gonorrhea 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 sub-trials, i.e., 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 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 on-line 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 randomization 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 gonorrhea 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 Supplement 1**) will be eligible to participate in the study. Prescriptions of these physicians for treatment of uncomplicated gonorrhea 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 gonorrhea, such as disseminated gonococcal infection and pelvic inflammatory disease (PID).

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 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 gonorrhea, 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 gonorrhea 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 gonorrhea 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 nonadherence (defined as having at least 25% of prescriptions nonadherent to the National Guidelines).

Sample size estimation

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

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

where $Z_{\alpha/2}$ is the critical value of the normal distribution at $\alpha/2$ (for a confidence level of 95%, α is 0.05 and the critical value is 1.96), Z_{β} is the critical value of the normal distribution at β (for a power of 90%, β is 0.1 and the critical value is 1.28); π_0 and π_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_{β} = 1.28, π_0 = 37.8% (based on a nationwide survey[18] in China), π_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 gonorrhea patients per hospital within six 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 randomization, a total of 144 hospitals will be recruited in the 8 provinces for the study (18 hospitals in each province).

Cluster randomization

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 randomization 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 8 participating provinces. After all 144 hospitals were randomized, one province will be randomly selected from the 8 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 (9 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**). Randomization is

conducted by an independent statistical analysts 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 (e.g. 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 Supplement 2**) and another baseline questionnaire survey to collect background information of the participating physicians (**see Supplement 3**) in both intervention and control groups for evaluating the appropriateness of randomization. A specific questionnaire survey (**see Supplement 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 (HIS), 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 Supplement 5 and Supplement 6**).

Data analysis

The data analysis methods are described in full detail in the accompanying data collection and analysis plan (**see Supplement 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 summarized 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% confidence interval 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 nonadherent to the National Guidelines as the physician with nonadherence, and then use multivariate logistic regression model to identify the independent variables associated with the nonadherence at a significant level of $p \leqslant 0.05$ and estimate adjusted odds ratio (AOR) 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 analyzed 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 authorized individuals for data analysis and reporting purposes only. Data will be entered into the database in an anonymized form to ensure confidentiality. Only principal investigator and other authorized 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.

Contributors

XSC: conceptualized the study. TTJ, YQY and XSC: designed the study. NXC and YPY: participated in the study design. TTJ: wrote the first draft of this protocol. XSC: made critical revision of the study protocol. YQY, NXC and YPY: contributed to the revision of the study protocol. All authors reviewed and approved the final manuscript.

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Disclaimer

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Competing interests

None declared.

Patient consent

Not required.

Ethics approval

Ethical approval for this study was obtained from the Chinese Academy of Medical Sciences Institute of Dermatology in Nanjing (2020-LS-004).

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Figure Legends

Figure 1. Flow chart of the cluster randomized controlled trial.

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

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

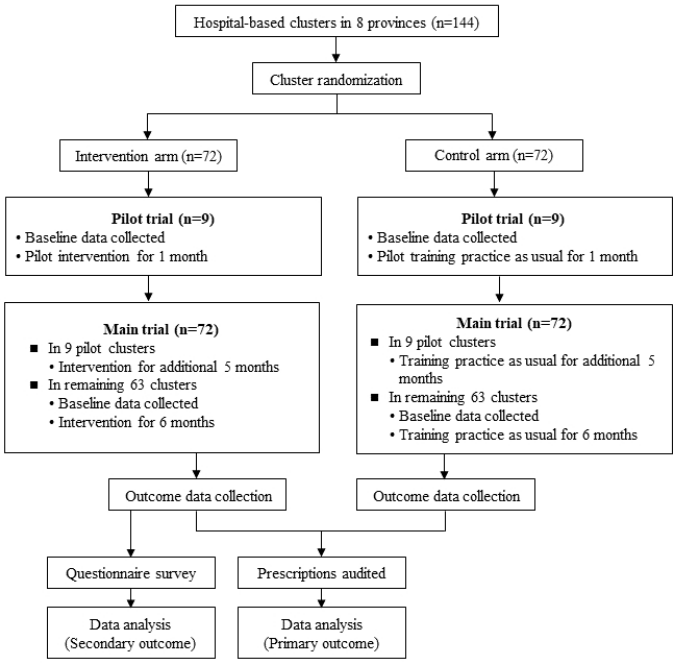

Figure 1

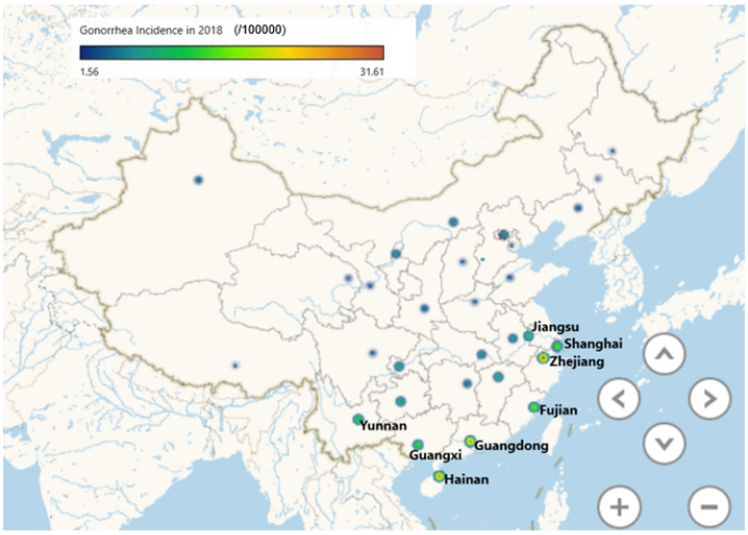

Figure 2

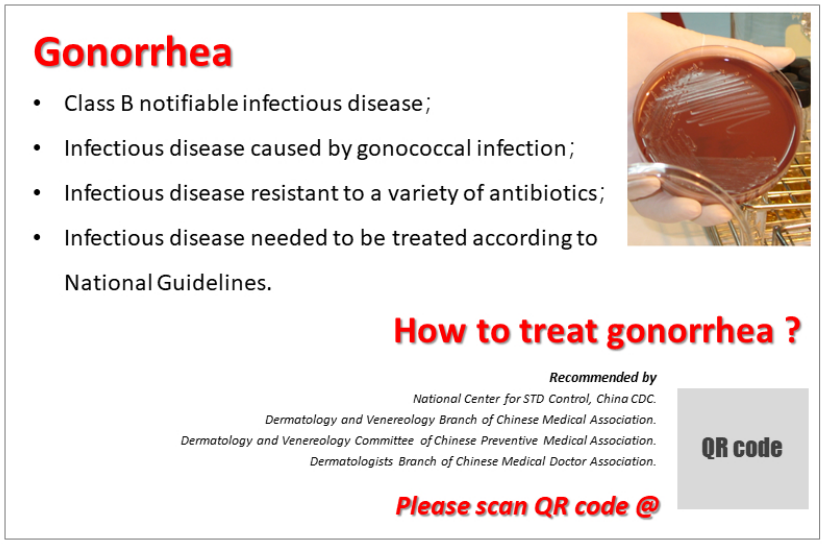

Figure 3

Supplement 1. Participant informed consent form

About this Study

You are being asked to take part in a research study that will help us better understand prescribing behavior for treatment of uncomplicated gonorrhea among physicians in China. Your participation in this project will allow us to develop better interventions to improve physicians' prescribing behaviors to follow the treatment guidelines.

What's involved?

Our study participants consist of physicians from eight provinces including Jiangsu, Shanghai, Zhejiang, Fujian, Guangdong, Guangxi, Hainan, and Yunnan. If you participate in this study, you will be asked to complete an online questionnaire. A subset of participants will be asked to complete an additional follow-up questionnaire. The questionnaires will ask you to provide sociodemographic information and information about your comment on the interventions we provided. In addition, your prescriptions for uncomplicated gonorrhea will be randomly selected and audited. In order to ensure that your privacy is protected, all of your online responses will be encrypted and securely transferred to our data servers.

Voluntary participation

A decision not to participate or to withdraw from participation will not affect your relationship with the hospital in any way.

Discomfort and risks

Our study does not introduce any additional risk or discomfort to participants.

Compensation

No financial incentives are offered for participating in the study.

Questions

All research on human volunteers is reviewed by a committee that works to protect your rights and welfare. If you have any questions about the research or your participation in the study, feel free to contact Ting-Ting Jiang (021-85478901).

Participant statement

○ I have been informed about this study and understand what is involved. I also know whom to contact if I need more information. I understand that confidentiality will be preserved. I agree to participate in this study.

Supplement 2. Hospital information

This form is used for collecting background information of the eligible hospitals for participating in the cluster randomized controlled trial. By providing this information, neither do you commit to participating in the trial nor is your hospital for sure allocated to a specific arm of the trial. It is guaranteed that confidentiality of this information can be ensured and the data from the information collection will be only used for anonymous analysis.
Thank you in advance for your time in providing this information.

Province: _____ **City:** _____ **Code:**_____(*Assigned*)

Hospital name: _____

Hospital nature: ☐General hospital; ☐ Specialized hospital; ☐ Community hospital;
☐ Other (Specific_____)

Hospital township: ☐ Public teaching hospital; ☐ Public non-teaching hospital;
☐ Private hospital; ☐ Other (Specific_____)

Hospital category: ☐ Primary hospital; ☐ Secondary hospital;
☐ Tertiary hospital; ☐ Uncategorized or others

Number of gonorrhea cases reported in the last year: _____

Department and staff: *Does the hospital have the following departments and how many doctors qualified are there in each department for managing patients with sexually transmitted infections?*

☐ Dermatology (dermatovenerology); Number of doctors: _____
☐ Urology; Number of doctors: _____
☐ Andrology; Number of doctors: _____
☐ Gynaecology; Number of doctors: _____

Availability of antibiotics: *Does this hospital stock the following antibiotics and what are their dosage forms?*

Ceftriaxone (injectable): ☐ 250mg; ☐ 500mg; ☐ 1g;
☐ 2g; ☐ Other (Specific:_____)
Spectinomycin (injectable): ☐ 2g; ☐ Other (Specific:_____)

Does the hospital agree to participate in the study? ☐ Yes; ☐ No

Supplement 3. Questionnaire survey for the physicians in the participating hospitals

This form is used for collecting socio-demographic information. You are invited to participate in this questionnaire survey which takes you about less than 5 minutes to answer all questions. By completing this questionnaire, you are not automatically required to commit to participating in the intervention trial later on. Participation in this survey is totally voluntary and you can choose either participation to answer all or some questions or rejection to participate. Any choice does not influence the relationship between you and the investigators.

Thank you in advance for your time in completing this questionnaire.

1. Your working number:

- ❍ □□□□ (*Assigned*)

2. Your gender:

- ❍ Male
- ❍ Female

3. Your age:

- ❍ <25
- ❍ 25~35
- ❍ 35~45
- ❍ 45~55
- ❍ 55~65
- ❍ >65

4. What is the highest degree that you have obtained?

- ❍ Post-Doctor
- ❍ Doctor
- ❍ Master
- ❍ Bachelor
- ❍ Other (Specific:_____)

5. What department are you working?

- ❍ Dermatology & STD
- ❍ Andrology
- ❍ Urology department
- ❍ Obstetrics and gynecology
- ❍ Other (Specific:_____)

7. How long have you been working in this department?

- ❍ ≤5 years
- ❍ 6~10 years
- ❍ ≥11 years

8. Your professional title is:

- ❍ Chief physician
- ❍ Associate chief physician
- ❍ Physician-in-charge
- ❍ Resident physician
- ❍ Other (Specific:_____)

9. In the last three months, approximately how many cases of uncomplicated gonorrhea have you treated?

- ❍ □□□□ (Number)

10. In the last three months, have you received relevant trainings on treatment of gonorrhea?

- ❍ Yes (Specific:_____)
- ❍ No

Supplement 4. Questionnaire survey for the physicians in the intervention hospitals

This form is used for collecting information after a cluster randomized controlled trials (RCT) is conducted at your hospital. You are invited to participate in this questionnaire survey which takes you about 10 minutes to answer all questions. Participation in this survey is totally voluntary and you can choose either participation to answer all or some questions or rejection to participate. Any choice does not influence the relationship between you and the investigators.
Thank you in advance for your time in considering this questionnaire survey or completing this questionnaire.

1. Your working number:

❍ □□□□ (*Assigned*)

2. Your gender:

❍ Male
❍ Female

3. Your age:

❍ <25
❍ 25~35
❍ 35~45
❍ 45~55
❍ 55~65
❍ >65

4. What is the highest education degree that you have obtained?

❍ Post-Doctor
❍ Doctor
❍ Master
❍ Bachelor
❍ Other (Specific:_____)

5. The name of hospital you are working at:

❍ _____(Text)

6. What department do you work in the hospital?

❍ Dermatology & STD

❍ Andrology

❍ Urology department

❍ Obstetrics and gynecology

❍ Other (Specific:_____)

7. How long have you been working in this department?

❍ ≤5 years

❍ 6~10 years

❍ ≥11 years

8. Your current professional title is:

❍ Chief physician

❍ Associate chief physician

❍ Physician-in-charge

❍ Resident physician

❍ Other (Specific:_____)

9. In the last three months, approximately how many cases of uncomplicated gonorrhea have you treated?

❍ _____(Number input) (If answer <1, Skip to End of Survey)

10. Before participating in the on-line video-based training, do you know about the up-to-dated National STD Treatment Guidelines for treatment of uncomplicated gonorrhea?

❍ Yes

❍ No

11. In the last six months, how many times did you access to the on-line training video developed on the WenJuanXing platform?

- ❍ 0
- ❍ 1~3
- ❍ 4~6
- ❍ ≥7

12. In the last six months, have you received other relevant trainings on treatment of gonorrhea?

- ❍ Yes (Specific:_____)
- ❍ No

13. What do you think about the up-to-dated regimen in the National STD Treatment Guidelines for treatment of uncomplicated gonorrhea using ceftriaxone 1g as a single dose?

- ❍ Appropriate (enough) dosage
- ❍ Dosage is overdose
- ❍ Dosage is not enough
- ❍ Difference from case to case
- ❍ Don't know

14. Do you think this on-line video-based training programme is helpful for improving your knowledge on management of gonorrhea?

- ❍ Very helpful
- ❍ Helpful
- ❍ Not helpful
- ❍ Don't know

15. Do you think the participation in this on-line video-based training programme every two months occupy too much of your time?

- ❍ Yes
- ❍ No

16. Will you continue to use this on-line video-based training programme?

- ❍ Yes
- ❍ No

17. Are you willing to recommend this on-line video-based training programme to other colleagues?

- ❍ Yes
- ❍ No

18. Do you have any suggestions on the on-line training programmes?

- ❍ Yes (Specific:_____)
- ❍ No

Supplement 5. Baseline data on prescriptions

This form is used for retrospectively collecting data derived from the eligible prescriptions PRIOR to the trial in each of departments in each of participating hospitals. It is guaranteed that confidentiality of these data can be ensured, and these data will be only used for anonymous analysis.

Thank you in advance for your time in providing these data.

Province: _____ **City:** _____ **Code:**_____(*Assigned*)

Hospital name: _____

Department:

☐ Dermatology (dermatovenerology)

☐ Urology

☐ Andrology

☐ Gynaecology

Prescription information

No.	Patient' gender	Patient's age	Diagnosis	Treatment			Physician's working number
				Drug	Dosage	Duration	
							□□□□
							□□□□
							□□□□
							□□□□
							□□□□
							□□□□
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							□□□□
							□□□□

Supplement 6. Endline data on prescriptions

This form is used for collecting data derived from the eligible prescriptions AFTER the trial in each of department in each of participating hospitals. It is guaranteed that confidentiality of these data can be ensured, and these data will be only used for anonymous analysis.
Thank you in advance for your time in providing these data.

Province: _____ **City:** _____ **Code:**_____(*Assigned*)

Hospital name: _____

Department: ☐ Dermatology (dermatovenerology)
☐ Urology
☐ Andrology
☐ Gynaecology

Prescription information

No.	Patient' gender	Patient's age	Diagnosis	Treatment			Physician's working number
				Drug	Dosage	Duration	
							□□□□
							□□□□
							□□□□
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Supplement 7. Data Collection and analysis plans prior to implementing the prospective cluster randomized controlled trial

The analyses presented in the current manuscript evolved from the following research question and associated data collection and analysis:

1. **How will we evaluate the appropriateness of randomization?**
   a) We will use questionnaires to collect the background information of participating hospitals (hospital's level, and category) and participating physicians (sex, age, education level, working year, department, and previous training).
   b) We will estimate the differences between the intervention and control arms in cluster (hospital)'s characteristics including level (capital vs. other city), and category (general vs. specialized hospital).
   c) We will compare the differences between the intervention and control arms in participating physician's characteristics including sex, age, education level, working year, department, and previous training.
2. **How will we evaluate the missing data?**
   a) We will define the physicians who provide informed consent and are willing to participate in the study and then withdraw from the intervention or are unwilling to have their prescriptions audited later on as missing participants.
   b) We will identify the missing participants from the complete dataset and define the data of these participants as missing data.
   c) We will compare the differences between the missing data and the data for analysis in participating physician's characteristics including sex, age, education level, working year, department, and previous training.
3. **What are the determinants used to describe the adherence rate to the National Guidelines and intervention effect for measuring the primary outcome?**
   a) We will collect the most recent 100 eligible prescriptions from each participating hospital (cluster) prior to intervention implementation period and 6 months after the implementation.

b) We will define the regimen of 1 g ceftriaxone described by the participating physician for treatment of uncomplicated gonorrhea as adherence to the National Guidelines (dichotomous outcome).

c) We will estimate the adherence rate and its 95% confidence intervals (CIs) using the total number of eligible prescriptions and the number of the prescriptions met the criteria of adherence.

d) We will estimate the intervention effect which is reported as rate ratio (RR) and 95% CIs compared with the control group. The stratum-specific endline adherence rate ratios will be calculated from the stratum-specific endline adherence rates (mean cluster-level outcomes) in each arm. The crude intervention effect as the overall endline adherence rate ratio between the intervention arm and control arm will be estimated from the weighted average of the stratum-specific endline adherence rate ratios, with weights that are inversely proportional to the stratum-specific variances. Formal testing of the null hypothesis that the overall adherence rate ratio is equal to 1 will be conducted using stratified t-test, and 95% confidence interval will be adjusted for between-cluster variance and stratification. To adjust for potentially important covariates, including cluster-level outcome at baseline, and additional patient (age [years], sex [male, female]), linked physician (age [years], sex [male, female], education level [bachelor degree or higher, other], working year [years], department [dermatology or dermatovenerology, other], previous training [yes, no]) and hospital (province located) factors, a two-stage adjusted analyses will be conducted. 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 individual-level model predicted values and the individual-level observed values will be used to calculate covariate-adjusted cluster-level ratio residuals. The covariate-adjusted ratio residuals will then be used in place of cluster specific proportions to conduct stratified t-test and calculate 95% confidence interval 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 analyses, considering adjusting increases power and reduces the effect of imbalances between arms with typically minimal risks.

e) We will calculate the differences over 6 months of the intervention in both intervention and control groups, respectively.

f) We will also conduct subgroup analyses on primary outcome to indicate the intervention effect across the subgroups in terms of hospitals [hospital's level, and category] and physicians [sex, age, education level, working year, department, and previous training]. The same main analysis approach planned above will be used for the cluster-level subgroup analyses to obtain estimates of the treatment effect, its 95% confidence interval and statistical significance within each subgroup. To estimate the statistical significance of any differences in treatment effect among subgroups, analysis of variance will be used on the cluster-level summary outcome data, with terms for treatment, subgroup and the interaction between treatment and subgroup.

4. How will we measure the barriers to non-adherence to the National Guidelines for measuring the secondary outcome?

a) We will collect the physician's information on socio-demographic characteristics, education background, working experience, and perceptions, attitudes, and practices using a questionnaire survey in the intervention hospitals.

b) We will define the physicians who have at least 25% prescriptions nonadherent to the National Guidelines as the physician with nonadherence.

c) We will use the nonadherence as dependent variables for the analyses to identify the factors influencing the nonadherence.

d) We will present descriptive statistics on the physician's socio-demographic characteristics, education background, working experience, and perceptions, attitudes, and practices.

e) We will use multivariate logistic regression model to explore the associations between key factors (physician's age [years], education level [bachelor degree or higher, other], working year [years], department [dermatology or dermatovenerology, other], on-line training video access times [≤ 3, > 3], perceptions on the National Guidelines [appropriate (enough) dosage, other], attitude on the training programme [very helpful or helpful, other]) and the nonadherence. These results will be presented as adjusted odds ratio (AOR), associated 95% CIs and p values. The factors included in the model will be determined theoretically, based on the literature and the findings of our qualitative work.

TIDieR
Template for Intervention Description and Replication

The TIDieR (Template for Intervention Description and Replication) Checklist*:

Information to include when describing an intervention and the location of the information

Item number	Item	Where located **	
		Primary paper (page or appendix number)	Other † (details)
	BRIEF NAME		
1.	Provide the name or a phrase that describes the intervention.	Page 8	
	WHY		
2.	Describe any rationale, theory, or goal of the elements essential to the intervention.	Page 8	
	WHAT		
3.	Materials: Describe any physical or informational materials used in the intervention, including those provided to participants or used in intervention delivery or in training of intervention providers. Provide information on where the materials can be accessed (e.g. online appendix, URL).	Page 8	
4.	Procedures: Describe each of the procedures, activities, and/or processes used in the intervention, including any enabling or support activities.	Page 8	
	WHO PROVIDED		
5.	For each category of intervention provider (e.g. psychologist, nursing assistant), describe their expertise, background and any specific training given.	Page 8	
	HOW		

6.	Describe the modes of delivery (e.g. face-to-face or by some other mechanism, such as internet or telephone) of the intervention and whether it was provided individually or in a group.	Page 8	
	WHERE		
7.	Describe the type(s) of location(s) where the intervention occurred, including any necessary infrastructure or relevant features.	Page 8	
	WHEN and HOW MUCH		
8.	Describe the number of times the intervention was delivered and over what period of time including the number of sessions, their schedule, and their duration, intensity or dose.	Page 8	
	TAILORING		
9.	If the intervention was planned to be personalised, titrated or adapted, then describe what, why, when, and how.	N/A	
	MODIFICATIONS		
10.‡	If the intervention was modified during the course of the study, describe the changes (what, why, when, and how).	N/A	
	HOW WELL		
11.	Planned: If intervention adherence or fidelity was assessed, describe how and by whom, and if any strategies were used to maintain or improve fidelity, describe them.		
12.‡	Actual: If intervention adherence or fidelity was assessed, describe the extent to which the intervention was delivered as planned.	Page 8 N/A	

** **Authors** - use N/A if an item is not applicable for the intervention being described. **Reviewers** – use '?' if information about the element is not reported/not sufficiently reported.

† If the information is not provided in the primary paper, give details of where this information is available. This may include locations such as a published protocol or other published papers (provide citation details) or a website (provide the URL).

‡ If completing the TIDieR checklist for a protocol, these items are not relevant to the protocol and cannot be described until the study is complete.

* We strongly recommend using this checklist in conjunction with the TIDieR guide (see *BMJ* 2014;348:g1687) which contains an explanation and elaboration for each item.
* The focus of TIDieR is on reporting details of the intervention elements (and where relevant, comparison elements) of a study. Other elements and methodological features of studies are covered by other reporting statements and checklists and have not been duplicated as part of the TIDieR checklist. When a **randomised trial** is being reported, the TIDieR checklist should be used in conjunction with the CONSORT statement (see www.consort-statement.org) as an extension of **Item 5 of the CONSORT 2010 Statement.** When a **clinical trial protocol** is being reported, the TIDieR checklist should be used in conjunction with the SPIRIT statement as an extension of **Item 11 of the SPIRIT 2013 Statement** (see www.spirit-statement.org). For alternate study designs, TIDieR can be used in conjunction with the appropriate checklist for that study design (see www.equator-network.org).

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

Section/item	ItemNo	Description	Addressed on page number
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	ChiCTR2000029591
	2b	All items from the World Health Organization Trial Registration Data Set	ChiCTR2000029591
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	12-13
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	1
	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	13

	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)	7
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	4-5
	6b	Explanation for choice of comparators	5
Objectives	7	Specific objectives or hypotheses	5
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)	5
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	5-6
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)	6-7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8

	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)	8
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	8
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
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	8-9
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)	7
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	9
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7
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	10
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	10
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10
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	N/A
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	10
	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	10

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	12
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	10-11, Supplement 7
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11
	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)	11
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	12
	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	11
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	7

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	12
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)	12
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
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	12
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
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	12
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	12
	31b	Authorship eligibility guidelines and any intended use of professional writers	12

	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	12
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplement 1
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	N/A

*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.