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

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1 **A novel education-based intervention to reduce inappropriate**
2 **antibiotic prescribing for treatment of gonorrhoea in China: protocol**
3 **for a cluster randomized controlled trial**

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16

17 **ABSTRACT**

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

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

38 **Ethics and dissemination:** Ethical approval was obtained from the Medical Ethics
39 Committee of the Chinese Academy of Medical Sciences Institute of Dermatology (2020-LS-
40 004) and all physicians will provide an informed consent prior to participation in the surveys.
41 The findings of the trial will be disseminated through conferences, peer-reviewed journals,
42 and developing training programmes for physicians.

44 **Keywords:** gonorrhoea, antibiotic, prescribing behavior, education, cluster randomized
45 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.

60 INTRODUCTION

61 Gonorrhoea, caused by *Neisseria gonorrhoeae* (*N. gonorrhoeae*), remains one of the most
62 common sexually transmitted diseases (STDs) worldwide. According to the most recent
63 World Health Organization (WHO) report in 2016, there were 86.9 million incident cases (15-
64 49 years of age) globally, which were more than 10% higher than that in 2012.¹ Left
65 untreated, the infection can cause serious medical problems, particularly for women,
66 including chronic pelvic pain, ectopic pregnancy, and even infertility.² In addition to
67 behavioral interventions to prevent becoming infected with this disease, timely detection of
68 the infection followed by effective treatment with antibiotics remain the mainstream strategy
69 for control of this infection. Unfortunately, *N. gonorrhoeae* has developed resistance to nearly
70 every antibiotic ever used to effectively treat it since sulphonamides were introduced as the
71 first drugs for this treatment in 1940s.³ Due to widespread emergence of the resistant strains,
72 only the extended-spectrum cephalosporin (ESC) and azithromycin which is usually used
73 with ceftriaxone in dual therapy are left to be recommended as first-line regimen for treatment
74 of gonorrhoea in most countries.⁴⁻⁷ However, in recent years, gonococcal strains with reduced
75 susceptibility or resistance to ESC and resistance to high-level azithromycin have been
76 identified from many countries including China⁸⁻⁹ and treatment failures with ceftriaxone
77 have been reported in Japan, Australia, European countries, Canada, and South Africa.¹⁰⁻¹³
78 The data from the China Gonococcal Resistance Surveillance Programme (China-GRSP)
79 indicated that 18.6% of clinical isolates were resistant to azithromycin and 9.7%-12.2% of
80 clinical isolates were less susceptible to ceftriaxone over the years of 2013 and 2016.¹⁴

81 It has been recognized that much of the antimicrobial resistance (AMR) of gonorrhoea
82 originates in Asia and then transmitted to the rest of world.¹⁵⁻¹⁶ Although many factors
83 contribute to the emergence of gonococcal AMR, inappropriate use (misuse or overuse) of
84 antibiotics for treatment of gonorrhoea in clinical practice in many countries in Asia may be
85 one of drivers for AMR due to antibiotic selective pressure. A recent study in China indicated
86 less than 1% of patients with uncomplicated gonorrhoea were treated following the ceftriaxone
87 regimen recommended by the national guidelines (ceftriaxone 250 mg intramuscular as a
88 single dose).¹⁷ More than 70% of the patients received a dosage of more than 1g for their
89 treatment.¹⁷ Several factors affect physicians' prescribing behaviors, including knowledge

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4 90 about the antibiotics, awareness of national guidelines, previous experience in treatment, and
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6 91 trust to the antibiotics. A nationwide survey in China revealed a higher adherence to the
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8 92 national guidelines for treatment of uncomplicated gonorrhoea among physicians who were
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10 93 aware of the guidelines than those who were not but the participation in training courses did
11
12 94 not significantly improve the prescribing behaviors,¹⁸ indicating that more innovative
13
14 95 interventions are needed to address the issues of inappropriate antibiotic use in treatment of
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16 96 gonorrhoea in China. To explore the innovative strategies to ensure appropriate use of
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18 97 antibiotics for treatment of gonorrhoea has been listed as one of priorities in a comprehensive
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20 98 research plan called the ROADMAP (Resistance surveillance, Outcomes due to AMR,
21
22 99 Antibiotic stewardship and application, Diagnostic tools, Mechanisms of AMR,
23
24 100 Antimicrobial assessment, and Population pharmacokinetics and pharmacodynamics) to
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26 101 address research needs for gonococcal AMR in China.¹⁹ For this purpose, we will conduct a
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28 102 prospective cluster randomized trial with a primary objective to observe whether the
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30 103 intervention arm could improve the adherence rate to the national guidelines above the control
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32 104 arm by 10% in antibiotic prescribing for treatment of uncomplicated gonorrhoea. Our
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34 105 secondary objectives are to identify factors related to nonadherence to national guidelines
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36 106 among participants in the intervention arm.

107 **METHODS AND ANALYSIS**

108 **Study design**

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

120 Study sites

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

125 Sample size estimation

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

$$127 \quad c = 1 + (Z_{\alpha/2} + Z_{\beta})^2 [\pi_0(1-\pi_0)/n + \pi_1(1-\pi_1)/n + k^2(\pi_0^2 + \pi_1^2)] / (\pi_0 - \pi_1)^2$$

128 where $Z_{\alpha/2}$ is the critical value of the normal distribution at $\alpha/2$ (for a confidence level of 95%,
 129 α is 0.05 and the critical value is 1.96), Z_{β} is the critical value of the normal distribution at β
 130 (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
 131 the control and intervention arms, respectively; n is the number of samples needed in each
 132 cluster, and k is the between-cluster coefficient of variation of the proportions between
 133 clusters within each arm.

134 We used the following parameters and assumptions to estimate the sample size: $Z_{\alpha/2} =$
 135 1.96, $Z_{\beta} = 1.28$, $\pi_0 = 37.8\%$ (baseline proportion of prescriptions that are adherent to the
 136 regimens for treatment of uncomplicated gonorrhoea recommended by the up-to-dated
 137 National Guidelines for Management of Sexually Transmitted Diseases (hereinafter referred
 138 to the National Guidelines)),²¹ $\pi_1 = 41.6\%$ (calculated by assuming at least 10% increase in
 139 adherence to the National Guidelines in intervention arm from the 37.8% in the control arm),
 140 $n = 100$, and $k = 0.1$.

141 By entering these parameter and assumptions into the above formula, it is indicated that a
 142 total of 60 hospitals per arm are needed. Considering a possibility to have 10% loss of data
 143 from illegible prescriptions and a necessity to do stratified randomization, a total of 144
 144 hospitals will be recruited in the 8 provinces for the study (72 each in the control and
 145 intervention arms). Within each study province, 18 hospitals, excluding national or province-
 146 level hospitals because such hospitals are believed to have incomparably better knowledge in
 147 case management than others within the province, with the high volume of reported
 148 gonorrhoea cases will be invited to participate in the study.

149 Cluster randomization

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4 150 Within each province, 18 hospitals will be stratified firstly by hospital characteristics and then
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6 151 randomly allocated to either intervention or control arm to ensure equal numbers of hospitals
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8 152 in the two study arms (allocation ratio of 1:1) (**Figure 1**). Randomization is conducted by
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10 153 independent statistical analysts using a computer program written in R (V.3.5.3).

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12 154 Although the participating physicians are impossible to be masked to the intervention
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14 155 assigned to them in the trial, the data analysts will be masked to the assignments.

15 156 **Eligibility for participation**

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17 157 Hospitals with the out-patient departments of dermatology (dermatovenerology), urology, or
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19 158 andrology and the storage of ceftriaxone and/or spectinomycin are eligible for participating in
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21 159 the study. Physicians from these departments who agree to participate in the study are eligible
22
23 160 to have their prescriptions audited for the prescribing adherence.

24 161 **Intervention and control**

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26
27 162 The proposed intervention to be validated in the study is aimed to improve the physicians'
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29 163 adherence to the National Guidelines by reducing inappropriate antibiotic prescribing for
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31 164 treatment of patients infected with *N. gonorrhoeae*. The intervention procedures include to
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33 165 introduce an on-line training video developed on the WenJuanXing platform to all physicians
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35 166 who work in the out-patient departments of dermatology (dermatovenerology), urology, and
36
37 167 andrology in the intervention hospitals. By scanning QR code on the information card (**Figure**
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39 168 **3**), physicians could access to the training video. The video covers the workflows and
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41 169 requirements to manage a patient with uncomplicated gonorrhoea, including diagnostic criteria
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43 170 and treatment recommendations in accordance with the National Guidelines, and provides the
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45 171 contact infection for enquiring any questions related to the diagnosis and treatment as well. A
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47 172 short interaction (usually less than 30 minutes) between a public health staff and the
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49 173 physicians to interpret the intervention will take place in each of the department by
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51 174 integrating it into the most recent monthly department meeting following the implementation
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53 175 of the intervention for six months. The physicians will be contacted by the public health staff
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55 176 every two months through WeChat to remind about video playback if necessary.

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57 177 In hospitals allocated to the control arm, physicians will continue to participate in their
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59 178 training programme if they conventionally do it and to prescribe antibiotics for treatment of
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179 gonorrhoea cases according to their own knowledge and believes.

180 **Outcomes**

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

190 **Data collection**

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

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

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

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

213 **Data analysis**

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

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

233 **Process evaluation**

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

240 **Patient and public involvement**

241 Patients and the public were not involved in the development of the research question or
242 outcome measures. Physicians will be involved during the conduct of the study by giving
243 feedback on their barriers to comply with the intervention during the pilot trial in order to
244 tailor the intervention.

245 **ETHICS AND DISSEMINATION**

246 The study protocol has been reviewed and approved by the Medical Ethics Committee of the
247 Chinese Academy of Medical Sciences Institute of Dermatology in Nanjing (2020-LS-004).
248 An amendment will be submitted to the Committee for review and approval if any changes
249 are made to the study protocol. Physicians will provide an informed consent prior to
250 participation in the baseline and evaluation surveys and an additional informed consent prior
251 to auditing their prescriptions. Participating physicians will be free to withdraw from the
252 study at any time. All questionnaires, prescription audits and other data sources will be kept
253 securely and available to authorized individuals for data analysis and reporting purposes only.
254 Data will be entered into the database in an anonymized form to ensure confidentiality. Only
255 principal investigator and other authorized personnel will have access to the final study
256 database. The findings of the trial will be disseminated through reports at the national and
257 international conferences, publishing at least two papers in the peer-reviewed journals, and
258 provision of evidence for developing the on-the-job training programmes for physicians who
259 provide services to patients with STD.

261 **Contributors**

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

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270 Disclaimer

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

273 Competing interests

274 None declared.

275 Patient consent

276 Not required.

277 Ethics approval

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

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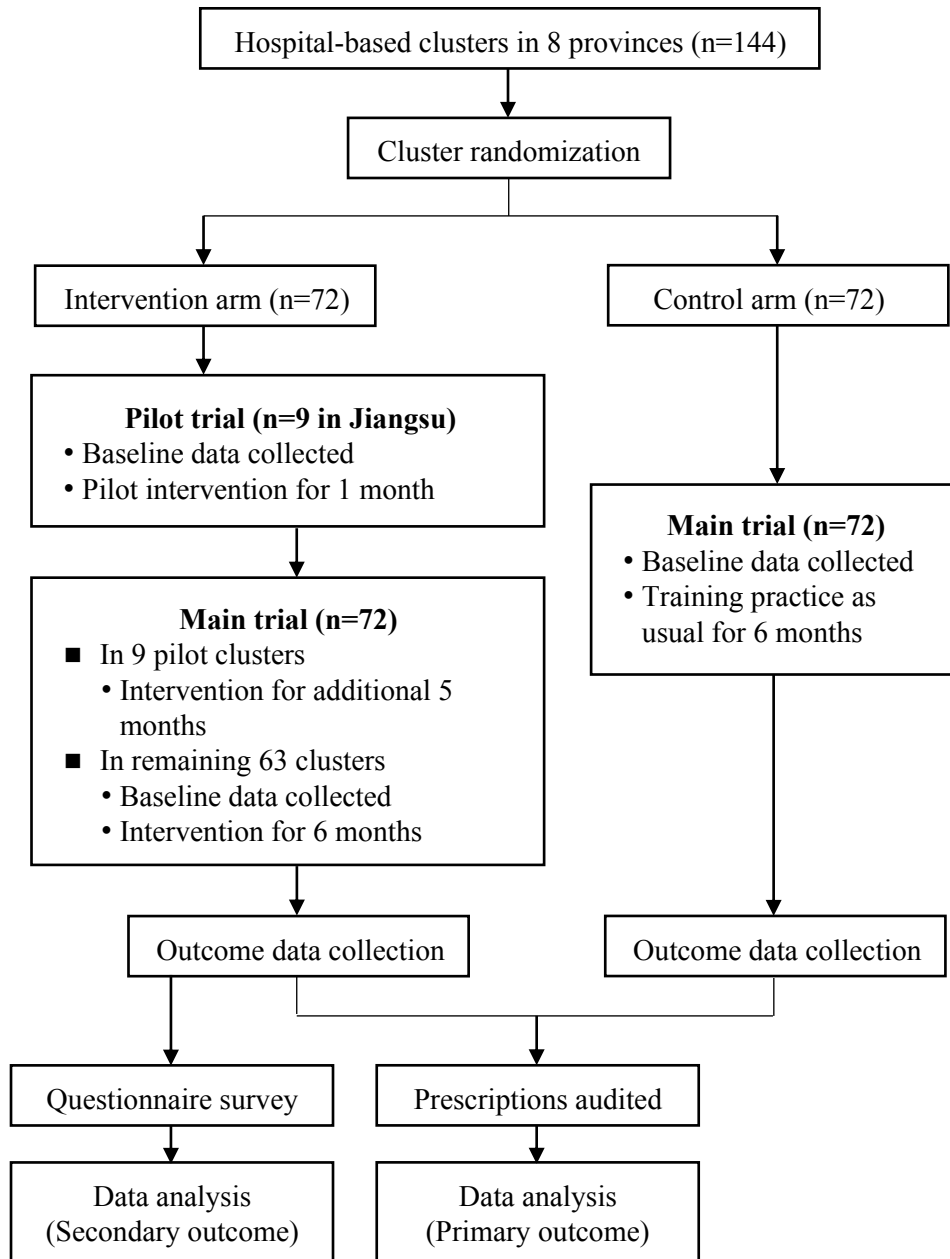
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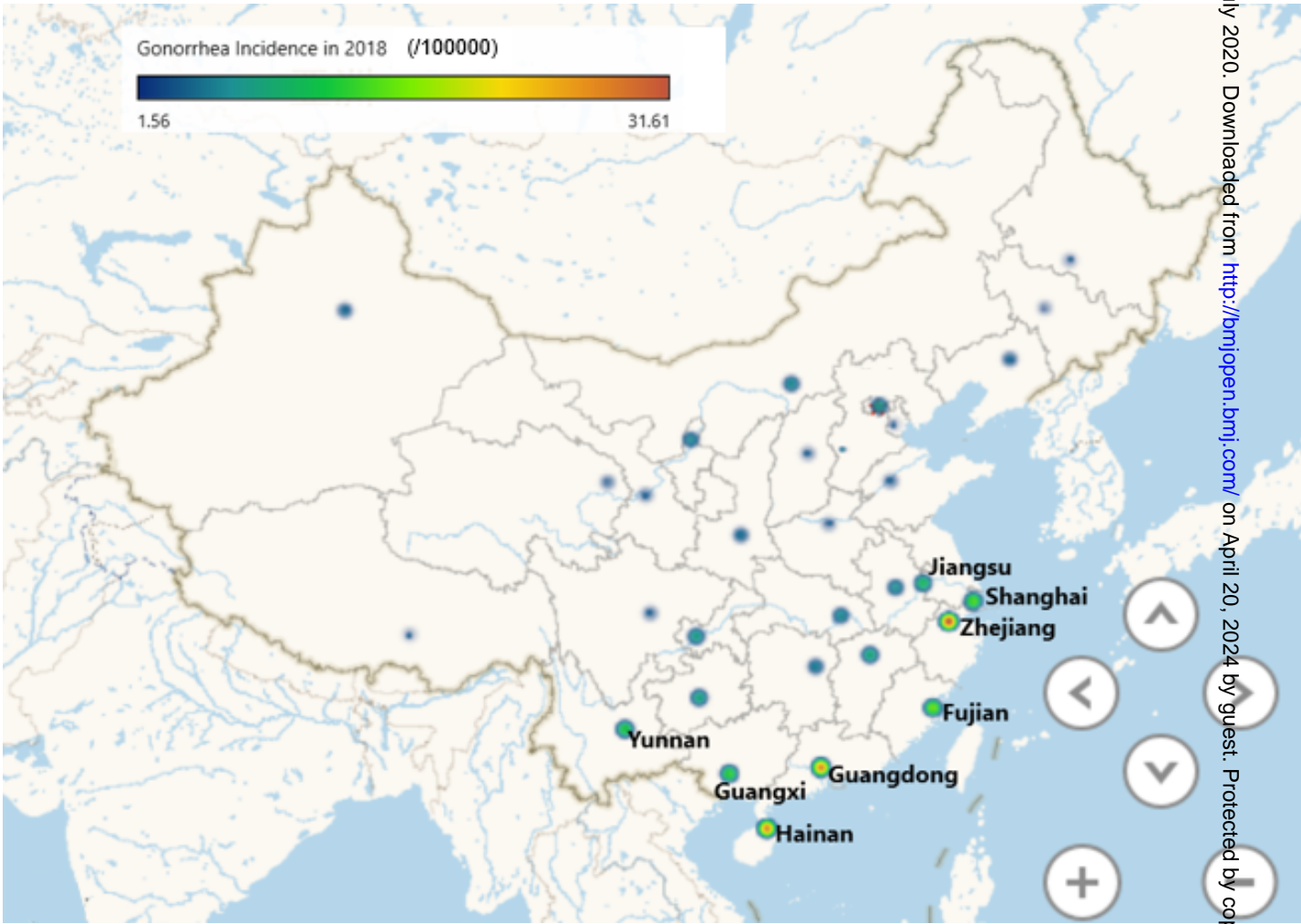
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10 **Figure 1.** Flow chart of the prospective cluster randomized trial.

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

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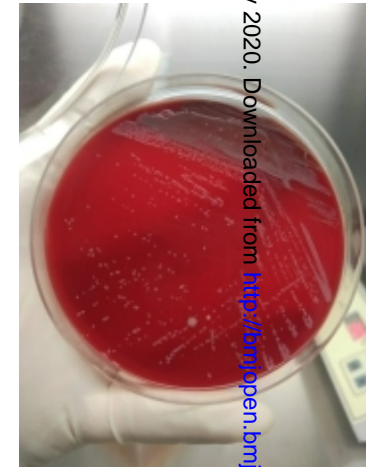
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Gonorrhoea

- 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 gonorrhoea ?

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.

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 gonorrhoea 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?

- 1
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- Dermatology & STD
 - Andrology
 - Urology department
 - Obstetrics and gynecology
 - Other (Specific: _____)

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

- ≤5 years
- 6~10 years
- ≥11 years

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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 gonorrhoea have you treated?

- _____ (Number)

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)

1
2
3 **5. What department do you work in the hospital?**
4

- 5 Dermatology & STD
6 Andrology
7 Urology department
8 Obstetrics and gynecology
9 Other (Specific: _____)
10
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15 **6. How long have you been working in this department?**
16

- 17 ≤5 years
18 6~10 years
19 ≥11 years
20
21
22
23

24 **7. Your current professional title is:**
25

- 26 Chief physician
27 Associate chief physician
28 Physician-in-charge
29 Resident physician
30 Other (Specific: _____)
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32
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36 **8. In the last three months, approximately how many cases of uncomplicated gonorrhea**
37 **have you treated?**
38

- 39 _____ (Number input) (If answer <1, Skip to End of Survey)
40
41
42
43

44 **9. In the last three months, which antibiotic was your first choice for treatment of**
45 **uncomplicated gonorrhea:**
46

- 47 Ceftriaxone (skip to 10)
48 Spectinomycin (skip to 11)
49 Cefotaxime (Skip to 12)
50 Azithromycin (Skip to 12)
51 Other (Specific: _____) (Skip to
52 12)
53
54
55
56
57

58 **10. In the last three months, which dose of ceftriaxone did you prefer to use for**
59 **treatment of uncomplicated gonorrhea:**
60

- 1
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8
9
- 0.25g
 - 0.5g
 - 1.0g
 - ≥ 2.0 g

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

- 15
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17
18
19
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21
22
23
- More effective
 - More convenient
 - Our clinic could not provide cephalosporin
 - Other (Specific: _____)
 - No applicable as I did not refer to prescribe spectinomycin

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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 gonorrhoea (ceftriaxone 500 mg, or spectinomycin 2 or 4 g IM as a single dose)?

- 30
31
32
33
- Yes
 - No

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

- 39
40
41
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43
44
45
- 0
 - 1~3
 - 4~6
 - ≥ 7

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

- 50
51
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- Yes (Specific: _____)
 - No

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

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12
- Appropriate (enough) dosage
 - Dosage is overdose
 - Dosage is not enough
 - Difference from case to case
 - Don't know

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

- 17
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19
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23
24
- Very helpful
 - Helpful
 - Not helpful
 - Don't know

25
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17. Do you think the participation in this on-line video-based training programme every two months occupy too much of your time?

- 29
30
31
32
33
- Yes
 - No

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35

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

- 36
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- Yes
 - No

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

- 45
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- Yes
 - No

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51

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

- 52
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- 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 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

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	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

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4		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)
5			6
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7			
8		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
9			8
10			
11		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
12			8
13			
14	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
15			9
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21	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)
22			Figure 1
23			
24			
25			
26	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
27			7
28			
29			
30	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size
31			7

Methods: Assignment of interventions (for controlled trials)

Allocation:

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4	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
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10	Allocation concealment	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
11	mechanism			
12				
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15	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
16				
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18	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
19				
20				
21		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
22				
23				
24				
25	Methods: Data collection, management, and analysis			
26	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
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33		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
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4	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
5				
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9	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
10				
11				
12		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	10
13				
14		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
15				
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19	Methods: Monitoring			
20				
21	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
22				
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25				
26		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
27				
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30	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
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34	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	6
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38	Ethics and dissemination			
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4	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	11
5				
6				
7	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
8				
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10				
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
12				
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14		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	11
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18	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
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22	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	12
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25	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
26				
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29	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
30				
31				
32	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
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37		31b	Authorship eligibility guidelines and any intended use of professional writers	11
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	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](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.

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BMJ Open

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

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Manuscript ID	bmjopen-2020-037549.R1
Article Type:	Protocol
Date Submitted by the Author:	15-Apr-2020
Complete List of Authors:	Jiang, Ting-Ting; Chinese Academy of Medical Sciences & Peking Union Medical College Hospital of Skin Diseases and Institute of Dermatology Yang, Yun-Qing; Guangzhou Institute of Dermatology Cao, Ning-Xiao; Chinese Academy of Medical Sciences & Peking Union Medical College Hospital of Skin Diseases and Institute of Dermatology Yin, Yue Ping; Chinese Academy of Medical Sciences & Peking Union Medical College Hospital of Skin Diseases and Institute of Dermatology, Reference laboratory Chen, Xiang-Sheng; Chinese Academy of Medical Sciences & Peking Union Medical College Hospital of Skin Diseases and Institute of Dermatology
Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Urology, Dermatology
Keywords:	Infectious diseases & infestations < DERMATOLOGY, Infection control < INFECTIOUS DISEASES, Urinary tract infections < UROLOGY

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1 **A novel education-based intervention to reduce inappropriate**
2 **antibiotic prescribing for treatment of gonorrhoea in China: protocol**
3 **for a cluster randomized controlled trial**

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5 Sheng Chen^{1,2}

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13
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15 Xiang-Sheng Chen; chenxs@ncstdlc.org

16

17 **ABSTRACT**

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

25 **Methods and analysis:** We will conduct a cluster randomized control trial (cluster-RCT)
26 across 144 hospitals (clusters) in 8 provinces in China. The intervention procedures will
27 include to introduce an on-line training video on WenJuanXing platform to all physicians who
28 work in the out-patient departments of dermatology (dermatovenerology), urology, andrology
29 or gynaecology. By scanning QR code, physicians could access to the training video. The
30 video covers workflows and requirements for managing a patient with uncomplicated
31 gonorrhoea, and provides the contact information for inquiring any questions as well. In
32 hospitals allocated to the control arm, physicians will continue to participate in their training
33 programme if they conventionally do it. The primary outcome is to estimate the proportion of
34 prescriptions adherent to the regimens (1g intramuscular ceftriaxone single dose)
35 recommended by the National Guidelines for treatment of uncomplicated gonorrhoea at the
36 cluster level. In addition, to understand physician's barriers to the intervention by conducting
37 a questionnaire survey will be considered as the secondary outcome of the study.

38 **Ethics and dissemination:** Ethical approval was obtained from the Medical Ethics
39 Committee of the Chinese Academy of Medical Sciences Institute of Dermatology (2020-LS-
40 004) and all physicians will provide an informed consent prior to participation in the surveys.
41 The findings of the trial will be disseminated through conferences, peer-reviewed journals,
42 and developing training programmes for physicians.

44 **Keywords:** gonorrhoea, antibiotic, prescribing behavior, education, cluster randomized
45 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.

60 INTRODUCTION

61 Gonorrhoea, caused by *Neisseria gonorrhoeae* (*N. gonorrhoeae*), remains one of the most
62 common sexually transmitted diseases (STDs) worldwide. According to the most recent
63 World Health Organization (WHO) report in 2016, there were 86.9 million incident cases (15-
64 49 years of age) globally, which were more than 10% higher than that in 2012.¹ Left
65 untreated, the infection can cause serious medical problems, particularly for women,
66 including chronic pelvic pain, ectopic pregnancy, and even infertility.² In addition to
67 behavioral interventions to prevent becoming infected with this disease, timely detection of
68 the infection followed by effective treatment with antibiotics remain the mainstream strategy
69 for control of this infection. Unfortunately, *N. gonorrhoeae* has developed resistance to nearly
70 every antibiotic ever used to effectively treat it since sulphonamides were introduced as the
71 first drugs for this treatment in 1940s.³ Due to widespread emergence of the resistant strains,
72 only the extended-spectrum cephalosporin (ESC) and azithromycin which is usually used
73 with ceftriaxone in dual therapy are left to be recommended as first-line regimen for treatment
74 of gonorrhoea in most countries.⁴⁻⁷ However, in recent years, gonococcal strains with reduced
75 susceptibility or resistance to ESC and resistance to high-level azithromycin have been
76 identified from many countries including China⁸⁻⁹ and treatment failures with ceftriaxone
77 have been reported in Japan, Australia, European countries, Canada, and South Africa.¹⁰⁻¹³
78 The data from the China Gonococcal Resistance Surveillance Programme (China-GRSP)
79 indicated that 18.6% of clinical isolates were resistant to azithromycin and 9.7%-12.2% of
80 clinical isolates were less susceptible to ceftriaxone over the years of 2013 and 2016.¹⁴

81 It has been recognized that much of the antimicrobial resistance (AMR) of gonorrhoea
82 originates in Asia and then transmitted to the rest of world.¹⁵⁻¹⁶ Although many factors
83 contribute to the emergence of gonococcal AMR, inappropriate use (misuse or overuse) of
84 antibiotics for treatment of gonorrhoea in clinical practice in many countries in Asia may be
85 one of drivers for AMR due to antibiotic selective pressure. A recent study in China indicated
86 less than 1% of patients with uncomplicated gonorrhoea were treated following the ceftriaxone
87 regimen recommended by the national guidelines (ceftriaxone 250 mg intramuscular as a
88 single dose).¹⁷ More than 70% of the patients received a dosage of more than 1g for their
89 treatment.¹⁷ Several factors affect physicians' prescribing behaviors, including knowledge

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4 90 about the antibiotics, awareness of national guidelines, previous experience in treatment, and
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6 91 trust to the antibiotics. A nationwide survey in China revealed a higher adherence to the
7
8 92 national guidelines for treatment of uncomplicated gonorrhoea among physicians who were
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10 93 aware of the guidelines than those who were not but the participation in training courses did
11
12 94 not significantly improve the prescribing behaviors,¹⁸ indicating that more innovative
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14 95 interventions are needed to address the issues of inappropriate antibiotic use in treatment of
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16 96 gonorrhoea in China. To explore the innovative strategies to ensure appropriate use of
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18 97 antibiotics for treatment of gonorrhoea has been listed as one of priorities in a comprehensive
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20 98 research plan called the ROADMAP (Resistance surveillance, Outcomes due to AMR,
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22 99 Antibiotic stewardship and application, Diagnostic tools, Mechanisms of AMR,
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24 100 Antimicrobial assessment, and Population pharmacokinetics and pharmacodynamics) to
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26 101 address research needs for gonococcal AMR in China.¹⁹

27 102 Mobile health (mHealth), defined as interventions and programmes designed to support
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29 103 medical and public health through the use of mobile technology, has been used as a tool to
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31 104 deliver continuous training and education to healthcare providers.²⁰⁻²¹ Previous randomized
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33 105 controlled trials (RCTs) in some medical fields have revealed the success of mHealth in
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35 106 optimizing antibiotic prescribing.²²⁻²⁴ However, there are no studies that shed light on whether
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37 107 such training programme is beneficial to improving antibiotic prescribing behaviors among
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39 108 physicians who provide treatment to patients with STDs. For this purpose, we will conduct a
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41 109 prospective cluster randomized trial with a primary objective to observe whether the proposed
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43 110 intervention (on-line video-based training programme) could significantly improve
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45 111 physicians' prescribing behaviors to adhere to the up-to-dated National Guidelines²⁵ in
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47 112 treatment of uncomplicated gonorrhoea (1g intramuscular ceftriaxone single dose). Our
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49 113 secondary objective is to understand physicians' barriers to the on-line video-based training
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51 114 programme.

52 115 **METHODS AND ANALYSIS**

53 116 **Study design and setting**

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56 117 The proposed study will use a cluster-randomized controlled trial design, consisting of two
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58 118 arms (**Figure 1**), to evaluate whether our intervention improves the physicians' adherence to
59
60 119 the National Guidelines in antibiotic prescribing for treatment of uncomplicated gonorrhoea.

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4 120 Selection of provinces for the study is based on the reported incidence of gonorrhoea in 2018.
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6 121 The 8 provinces (Jiangsu, Shanghai, Zhejiang, Fujian, Guangdong, Guangxi, Hainan and
7
8 122 Yunnan) are purposively selected from 31 provinces in mainland China in consideration of
9
10 123 their higher incidence of reported gonorrhoea cases than the national average (**Figure 2**).

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12 124 Within each study province, we will invite the city-level hospitals with the high volume
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14 125 of reported gonorrhoea cases to participate in the study. The hospitals at national or province-
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16 126 level in the study provinces will be excluded because small number of such hospitals within a
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18 127 province makes a difficulty to ensure comparable assignments of these hospitals into
19
20 128 intervention and control arms. Hospitals will be used for randomization of them into
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22 129 intervention or control arm, with randomization stratified by province considering the
23
24 130 potential for important variation in outcomes between the provinces. Core elements of the
25
26 131 intervention are on-line training on antibiotic prescribing for treatment of uncomplicated
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28 132 gonorrhoea among physicians working in the department of dermatology (dermatovenerology),
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30 133 urology, andrology or gynaecology in the intervention arm hospitals. A clustered design is
31
32 134 used to avoid the risk of contamination between different physicians within hospitals.

33
34 135 The study will be divided into two sub-trials, i.e., pilot and main trials. The internal pilot
35
36 136 trial will be conducted in one province randomly selected from the 8 study provinces to
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38 137 collect the data simultaneously in 9 intervention and 9 control hospitals during a period of one
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40 138 month for examining feasibility and acceptability of the intervention. If more than 60% of
41
42 139 physicians are willing to accept the intervention, the internal pilot hospitals and their outcome
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44 140 data will then become part of the main trial, and will be followed up for a further 5 months
45
46 141 (**Figure 1**). The remaining hospitals will be enrolled into the main trial and followed up for 6
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48 142 months (in other words, data collection in the pilot and main trial hospitals will finish at
49
50 143 different times). An independent advisory group consisting of key investigators, programme
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52 144 manager, hospital representatives and statistician will be established to oversee the trial
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54 145 implementation, review the study progress and provide the corresponding advices.

54 146 **Participants, recruitment and consent**

55
56 147 The study is planned to start in October 2020 and end by July 2021. The hospital selection
57
58 148 and project coordinator recruitment will take place in October 2020. Baseline assessments
59
60 149 will be carried out before randomization between November and December 2020. The

150 internal pilot trial will be conducted in January 2021. The intervention programme will be
151 administered from February to July 2021 followed by a questionnaire survey in intervention
152 hospitals in August 2021.

153 City-level hospitals with high volume of reported gonorrhoea cases are eligible for
154 participating in the study. Our investigators will prepare a list of eligible hospitals in each of
155 the 8 study provinces. These hospitals will be invited to participate in the study by explaining
156 the objectives and processes of the study to the hospitals' administrators and the in-hospital
157 project coordinators. If the hospital agree to participate in the study, the in-hospital project
158 coordinator will work together with the study investigators to invite physicians to participate
159 in the study. Physicians who work in the out-patient departments of dermatology
160 (dermatovenerology), urology, andrology or gynaecology and provide informed consent (**see**
161 **Supplement 1**) will be eligible for participating in the study. Prescriptions of these physicians
162 for treatment of uncomplicated gonorrhoea will be eligible for evaluating the adherence to the
163 National Guidelines, but prescriptions will be excluded from data analysis if they are
164 prescribed to the patients who meet any of the following criteria: (1) being younger than 18
165 years; (2) being pregnant or lactating woman; (3) being allergic to cephalosporin or penicillin
166 or having contraindication to cephalosporin ; (4) being treated with antibiotics for other
167 infections; or (5) being diagnosed as complicated gonorrhoea, such as disseminated gonococcal
168 infection and pelvic inflammatory disease (PID).

169 **Intervention and control**

170 The proposed intervention to be validated in the study is aimed to improve the physicians'
171 adherence to the National Guidelines by reducing inappropriate antibiotic prescribing for
172 treatment of patients infected with *N. gonorrhoeae*. Our research team have designed an
173 information card (**Figure 3**) to be distributed to all participating physicians in the intervention
174 arm hospitals by surface mail. By scanning QR code on the information card (**Figure 3**),
175 physicians could access to an on-line training video developed on the internet platform of
176 WenJuanXing (<https://www.wjx.cn/>). The video covers the workflows and requirements to
177 manage a patient with uncomplicated gonorrhoea, including diagnostic criteria and treatment
178 recommendations in accordance with the National Guidelines, and provides the contact
179 infection for enquiring any questions related to the diagnosis and treatment as well.

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

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

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

193 **Outcomes**

194 The primary outcome is the proportion of prescriptions adherent to the regimens for treatment
195 of uncomplicated gonorrhoea recommended by the National Guidelines at the cluster level.

196 The most recent 100 eligible prescriptions will be obtained by the prescription assessors from
197 each study hospital prior to implementation of the intervention as baseline data and 6 months
198 after the implementation for evaluating the outcome.

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

203 **Sample size estimation**

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

$$205 \quad c = 1 + (Z_{\alpha/2} + Z_{\beta})^2 [\pi_0(1-\pi_0)/n + \pi_1(1-\pi_1)/n + k^2(\pi_0^2 + \pi_1^2)] / (\pi_0 - \pi_1)^2$$

206 where $Z_{\alpha/2}$ is the critical value of the normal distribution at $\alpha/2$ (for a confidence level of 95%,
207 α is 0.05 and the critical value is 1.96), Z_{β} is the critical value of the normal distribution at β
208 (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
209 the control and intervention arms, respectively; n is the number of samples needed in each

210 cluster, and k is the between-cluster coefficient of variation of the proportions between
211 clusters within each arm.

212 We used the following parameters and assumptions to estimate the sample size: $Z_{\alpha/2} =$
213 1.96, $Z_{\beta} = 1.28$, $\pi_0 = 37.8\%$ (based on a nationwide survey¹⁸ in China), $\pi_1 = 41.6\%$ (based on
214 a consultation of STD clinical experts and control programmers, a minimum 10% increase in
215 adherence to the National Guidelines is deemed clinically relevant in the intervention arm), n
216 = 100 (minimum number of uncomplicated gonorrhoea patients per hospital within six
217 months), and $k = 0.1$ (based on a nationwide survey¹⁸ in China).

218 By entering these parameter and assumptions into the above formula, it is indicated that a
219 total of 60 hospitals per arm are needed. Considering a possibility to have 10% loss of data
220 and a necessity to do stratified randomization, a total of 144 hospitals will be recruited in the
221 8 provinces for the study (18 hospitals in each province).

222 **Cluster randomization**

223 Within each province, we will stratify the hospitals (clusters) into two groups (provincial
224 capital city and other cities), and 4 hospitals from capital city and 14 hospital from other cities
225 will be purposively selected in consideration of a high volume of reported cases. In each
226 stratification, a simple randomization process will be used to assign the hospitals into
227 intervention or control arm. Thus, we will have 72 hospitals assigned to the control group and
228 72 to the intervention group, 9 and 9 respectively for each one of the 8 provinces participating
229 in our study. After all 144 hospitals were randomized, one province will be randomly selected
230 from the 8 participating provinces to become the internal pilot area using closed and opaque
231 envelopes by an independent person from the research team, thus the 18 participating
232 hospitals (9 from each arm) in this selected province will become the internal pilot clusters.
233 The remaining 126 hospitals (63 from each arm) will, therefore, participate in the main trial,
234 along with the 18 hospitals involved in the internal pilot (**Figure 1**). Randomization is
235 conducted by independent statistical analysts using a computer program written in R
236 (V.3.5.3).

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

240 coordinators). However, the prescription assessors and data analyst will not be aware of the
241 assignments. Moreover, the patients will not be informed of the physician's status in the
242 control or intervention arm.

243 **Data collection**

244 Physicians' names will never appear in any datasets of the study but the physician who
245 participates in the study will be assigned a 4-digit working number by the project coordinators
246 and use this number as a study code in the questionnaire surveys and prescription audits. This
247 number will be only known by the project coordinator and used to match the questionnaire
248 surveys and prescription audits.

249 Prior to implementation of the intervention, we will have a baseline survey to collect
250 background information of the participating hospitals (**see Supplement 2**) and another
251 baseline questionnaire survey to collect background information of the participating
252 physicians (**see Supplement 3**) in both intervention and control groups for evaluating the
253 appropriateness of randomization. A specific questionnaire survey (**see Supplement 4**) will
254 be conducted among the physicians in the intervention hospitals after implementing the
255 intervention to collect data for measuring the secondary outcome.

256 Based on the Hospital Information System (HIS), our investigators (prescription assessors)
257 will screen the prescription to obtain the most recent 100 eligible prescriptions from each
258 participating hospital prior to intervention implementation period and 6 months after the
259 implementation, and extract patient's characteristics, diagnoses and medications, as well as
260 linked prescribing physician's name, using a data collection form (**see Supplement 5 and
261 Supplement 6**).

262 **Data analysis**

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

268 The characteristics of the participating hospitals (hospital level, hospital category) and
269 the participating physicians (including sex, age, education level, working year, department,

270 and previous training) will be summarized using frequencies (plus sample sizes) and means
271 (plus SDs) as appropriate for each group.

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

291 **Process evaluation**

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

298 **Patient and public involvement**

299 Patients and the public were not involved in the development of the research question or

300 outcome measures. Physicians will be involved during the conduct of the study by giving
301 feedback on their barriers to comply with the intervention during the pilot trial in order to
302 tailor the intervention.

303 **ETHICS AND DISSEMINATION**

304 The study protocol has been reviewed and approved by the Medical Ethics Committee of the
305 Chinese Academy of Medical Sciences Institute of Dermatology in Nanjing (2020-LS-004).
306 An amendment will be submitted to the Committee for review and approval if any changes
307 are made to the study protocol. All questionnaires, prescription audits and other data sources
308 will be kept securely and available to authorized individuals for data analysis and reporting
309 purposes only. Data will be entered into the database in an anonymized form to ensure
310 confidentiality. Only principal investigator and other authorized personnel will have access to
311 the final study database. The findings of the trial will be disseminated through reports at the
312 national and international conferences, publishing at least two papers in the peer-reviewed
313 journals, and provision of evidence for developing the on-the-job training programmes for
314 physicians who provide services to patients with STD.

316 **Contributors**

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

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325 National Clinical Research Center [2019060001].

326 **Disclaimer**

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

329 **Competing interests**

330 None declared.

331 **Patient consent**

332 Not required.

333 **Ethics approval**

334 Ethical approval for this study was obtained from the Chinese Academy of Medical Sciences

335 Institute of Dermatology in Nanjing (2020-LS-004).

336

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3 415 **Figure Legends**
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6 416 **Figure 1.** Flow chart of the prospective cluster randomized trial.
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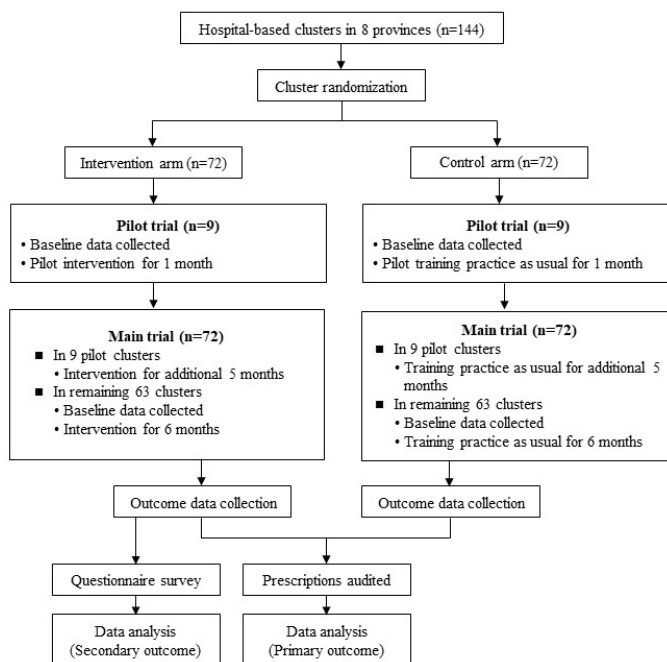
9 418 **Figure 2.** Reported incidence rate of gonorrhoea in 2018 in 31 provinces, autonomous regions,
10 and municipalities in the mainland of China.
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15 421 **Figure 3.** The information card with a QR code (hosted by WenJuanXing) to be distributed to
16 physicians in the intervention arm hospitals.
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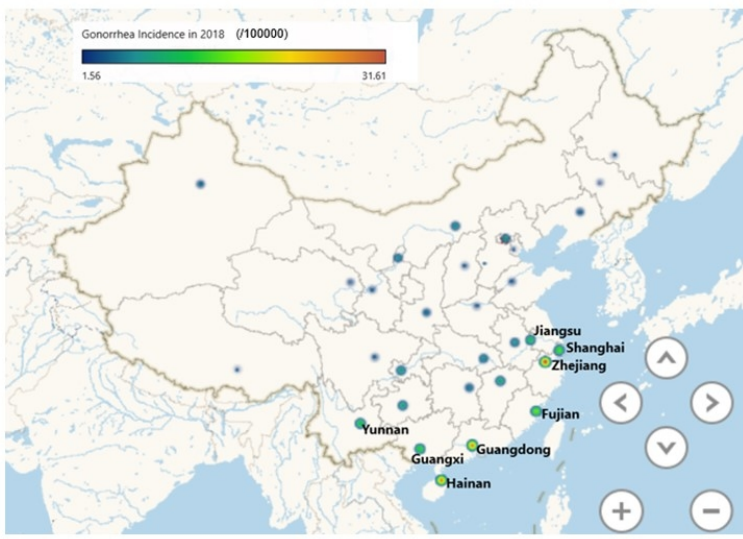
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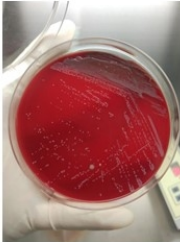


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Gonorrhoea

- 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 gonorrhoea ?

*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 subcommittee of Dermatologists Branch of Chinese Medical Doctor Association.*



Please scan QR code @

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 gonorrhoea 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 gonorrhoea 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 gonorrhoea 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?

- 1
2
3
4
5
6
7
8
9
10
11
12
- Dermatology & STD
 - Andrology
 - Urology department
 - Obstetrics and gynecology
 - Other (Specific: _____)

13
14

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

- 15
16
17
18
19
20
21
22
- ≤5 years
 - 6~10 years
 - ≥11 years

23
24

8. Your professional title is:

- 25
26
27
28
29
30
31
32
33
- Chief physician
 - Associate chief physician
 - Physician-in-charge
 - Resident physician
 - Other (Specific: _____)

34
35
36
37

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

- 38
39
40
- (Number)

41
42
43
44

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

- 45
46
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- 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: _____)

1
2
3 **5. The name of hospital you are working at:**
4

- 5 _____ (Text)
6
7

8
9 **6. What department do you work in the hospital?**

- 10 Dermatology & STD
11 Andrology
12 Urology department
13 Obstetrics and gynecology
14 Other (Specific: _____)
15
16
17
18
19

20
21 **7. How long have you been working in this department?**
22

- 23 ≤5 years
24 6~10 years
25 ≥11 years
26
27
28

29
30 **8. Your current professional title is:**
31

- 32 Chief physician
33 Associate chief physician
34 Physician-in-charge
35 Resident physician
36 Other (Specific: _____)
37
38
39
40
41

42 **9. In the last three months, approximately how many cases of uncomplicated gonorrhoea**
43 **have you treated?**
44

- 45 _____ (Number input) (If answer <1, Skip to End of Survey)
46
47
48

49 **10. Before participating in the on-line video-based training, do you know about the up-**
50 **to-dated National STD Treatment Guidelines for treatment of uncomplicated**
51 **gonorrhoea?**
52
53

- 54 Yes
55 No
56
57
58
59
60

1
2
3 **11. In the last six months, how many times did you access to the on-line training video**
4 **developed on the WenJuanXing platform?**

- 5
6
7 0
8 1~3
9
10 4~6
11
12 ≥ 7
13

14
15 **12. In the last six months, have you received other relevant trainings on treatment of**
16 **gonorrhoea?**

- 17
18
19 Yes (Specific: _____)
20
21 No
22

23
24 **13. What do you think about the up-to-dated regimen in the National STD Treatment**
25 **Guidelines for treatment of uncomplicated gonorrhoea using ceftriaxone 1g as a single**
26 **dose?**

- 27
28
29 Appropriate (enough) dosage
30
31 Dosage is overdose
32
33 Dosage is not enough
34
35 Difference from case to case
36
37 Don't know
38

39
40 **14. Do you think this on-line video-based training programme is helpful for improving**
41 **your knowledge on management of gonorrhoea?**

- 42
43 Very helpful
44
45 Helpful
46
47 Not helpful
48
49 Don't know
50

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

- 1
2
3 Yes
4
5 No
6
7

8 **16. Will you continue to use this on-line video-based training programme?**
9

- 10 Yes
11
12 No
13
14

15
16 **17. Are you willing to recommend this on-line video-based training programme to other**
17 **colleagues?**
18

- 19 Yes
20
21 No
22
23

24
25 **18. Do you have any suggestions on the on-line training programmes?**
26

- 27 Yes (Specific: _____)
28
29 No
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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.

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2
3 b) We will define the regimen of 1 g ceftriaxone described by the participating
4 physician for treatment of uncomplicated gonorrhoea as adherence to the
5 National Guidelines (dichotomous outcome).
6
7
8 c) We will estimate the adherence rate and its 95% confidence intervals (CIs)
9 using the total number of eligible prescriptions and the number of the
10 prescriptions met the criteria of adherence.
11
12
13 d) We will estimate the intervention effect which is reported as rate ratio (RR)
14 and 95% CIs compared with the control group. The stratum-specific endline
15 adherence rate ratios will be calculated from the stratum-specific endline
16 adherence rates (mean cluster-level outcomes) in each arm. The crude
17 intervention effect as the overall endline adherence rate ratio between the
18 intervention arm and control arm will be estimated from the weighted
19 average of the stratum-specific endline adherence rate ratios, with weights
20 that are inversely proportional to the stratum-specific variances. Formal
21 testing of the null hypothesis that the overall adherence rate ratio is equal to 1
22 will be conducted using stratified t-test, and 95% confidence interval will be
23 adjusted for between-cluster variance and stratification. To adjust for
24 potentially important covariates, including cluster-level outcome at baseline,
25 and additional patient (age [years], sex [male, female]), linked physician (age
26 [years], sex [male, female], education level [bachelor degree or higher,
27 other], working year [years], department [dermatology or
28 dermatovenerology, other], previous training [yes, no]) and hospital
29 (province located) factors, a two-stage adjusted analyses will be conducted.
30 We will fit a logistic regression model to the individual-level binary outcome
31 data including all covariates of interest as fixed effects, but without adjusting
32 for the treatment effect. The individual-level model predicted values and the
33 individual-level observed values will be used to calculate covariate-adjusted
34 cluster-level ratio residuals. The covariate-adjusted ratio residuals will then
35 be used in place of cluster specific proportions to conduct stratified t-test and
36 calculate 95% confidence interval using the above methods. Statistical
37 significance will be based on the (two-sided) p value estimated for the
38 primary outcome obtained from the covariate-adjusted analyses, considering
39 adjusting increases power and reduces the effect of imbalances between arms
40 with typically minimal risks.
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3 e) We will calculate the differences over 6 months of the intervention in both
4 intervention and control groups, respectively.
5
6 f) We will also conduct subgroup analyses on primary outcome to indicate the
7 intervention effect across the subgroups in terms of hospitals [hospital's
8 level, and category] and physicians [sex, age, education level, working year,
9 department, and previous training]. The same main analysis approach
10 planned above will be used for the cluster-level subgroup analyses to obtain
11 estimates of the treatment effect, its 95% confidence interval and statistical
12 significance within each subgroup. To estimate the statistical significance of
13 any differences in treatment effect among subgroups, analysis of variance
14 will be used on the cluster-level summary outcome data, with terms for
15 treatment, subgroup and the interaction between treatment and subgroup.
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24 **4. How will we measure the barriers to non-adherence to the National** 25 **Guidelines for measuring the secondary outcome?** 26

- 27 a) We will collect the physician's information on socio-demographic
28 characteristics, education background, working experience, and perceptions,
29 attitudes, and practices using a questionnaire survey in the intervention
30 hospitals.
31
32 b) We will define the physician who have at least 25% prescriptions
33 nonadherent to the National Guidelines as the physicians with nonadherence.
34
35 c) We will use the nonadherence as dependent variables for the analyses to
36 identify the factors influencing the nonadherence.
37
38 d) We will use bivariate analyses to test associations between each of
39 independent variables (socio-demographic characteristics, education
40 background, working experience, and perceptions, attitudes, and practices)
41 and the nonadherence (dependent variable). Independent variables with
42 significance level of $p < 0.10$ will be included in multivariate logistic
43 regression model.
44
45 e) We will use multivariate logistic regression model to identify the
46 independent variables associated with the nonadherence at a significant level
47 of $p \leq 0.05$ and estimate adjusted odds ratio (AOR) and its 95% CIs by
48 adjusting for potential confounding factors.
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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			

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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. WHERE	<u>Page 8-9</u>	_____
7.	Describe the type(s) of location(s) where the intervention occurred, including any necessary infrastructure or relevant features.	<u>Page 8-9</u>	_____
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. TAILORING	<u>Page 8-9</u>	_____
9.	If the intervention was planned to be personalised, titrated or adapted, then describe what, why, when, and how. MODIFICATIONS	<u>N/A</u>	_____
10.*	If the intervention was modified during the course of the study, describe the changes (what, why, when, and how). HOW WELL	<u>N/A</u>	_____
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.	<u>Page 8-9</u>	_____
12.*	Actual: If intervention adherence or fidelity was assessed, describe the extent to which the intervention was delivered as planned.	<u>N/A</u>	_____

** **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.

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5 † 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
6 published protocol or other published papers (provide citation details) or a website (provide the URL).

7 ‡ If completing the TIDieR checklist for a protocol, these items are not relevant to the protocol and cannot be described until the study is
8 complete.
9

10
11 * We strongly recommend using this checklist in conjunction with the TIDieR guide (see *BMJ* 2014;348:g1687) which contains an explanation
12 and elaboration for each item.

13
14 * The focus of TIDieR is on reporting details of the intervention elements (and where relevant, comparison elements) of a study. Other elements
15 and methodological features of studies are covered by other reporting statements and checklists and have not been duplicated as part of the
16 TIDieR checklist. When a **randomised trial** is being reported, the TIDieR checklist should be used in conjunction with the CONSORT
17 statement (see www.consort-statement.org) as an extension of **Item 5 of the CONSORT 2010 Statement**. When a **clinical trial protocol** is
18 being reported, the TIDieR checklist should be used in conjunction with the SPIRIT statement as an extension of **Item 11 of the SPIRIT 2013**
19 **Statement** (see www.spirit-statement.org). For alternate study designs, TIDieR can be used in conjunction with the appropriate checklist for
20 that study design (see www.equator-network.org).
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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

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	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

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5		11b	Criteria for discontinuing or modifying allocated interventions for a given	
6			trial participant (eg, drug dose change in response to harms, participant	8
7			request, or improving/worsening disease)	
8				
9		11c	Strategies to improve adherence to intervention protocols, and any	
10			procedures for monitoring adherence (eg, drug tablet return, laboratory	8-9
11			tests)	
12				
13		11d	Relevant concomitant care and interventions that are permitted or	
14			prohibited during the trial	9
15				
16	Outcomes	12	Primary, secondary, and other outcomes, including the specific	
17			measurement variable (eg, systolic blood pressure), analysis metric (eg,	
18			change from baseline, final value, time to event), method of aggregation	9
19			(eg, median, proportion), and time point for each outcome. Explanation	
20			of the clinical relevance of chosen efficacy and harm outcomes is strongly	
21			recommended	
22				
23	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and	
24			washouts), assessments, and visits for participants. A schematic diagram is	7-8
25			highly recommended (see Figure)	
26				
27	Sample size	14	Estimated number of participants needed to achieve study objectives and	
28			how it was determined, including clinical and statistical assumptions	9-10
29			supporting any sample size calculations	
30				
31	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target	
32			sample size	8

Methods: Assignment of interventions (for controlled trials)

Allocation:

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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

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5	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
6				
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10	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
11				
12				
13				
14		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	12
15				
16		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
17				
18				
19	Methods: Monitoring			
20				
21	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
22				
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27		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
28				
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31	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
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35	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	7
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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

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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

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

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1 **A novel education-based intervention to reduce inappropriate**
2 **antibiotic prescribing for treatment of gonorrhoea in China: protocol**
3 **for a cluster randomized controlled trial**

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16

17 **ABSTRACT**

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

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

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

40
41 **Keywords:** gonorrhoea, antibiotic, prescribing behavior, education, cluster randomized
42 controlled trial

43

44 **Strengths and limitations of this study**

- 45 ➤ The study design (cluster randomized controlled trial, cluster-RCT) is a robust
- 46 methodology to assess the effectiveness of behavioral interventions.
- 47 ➤ The study will be carried out in eight different provinces in China, thus will provide
- 48 insights on whether the intervention can be implemented in different local contexts.
- 49 ➤ The questionnaire administered to physicians prior to the intervention may influence the
- 50 prescribing behaviors of physicians from hospitals in the control arm, which may
- 51 undermine the effect of intervention.

52
53 **Trial registration number ChiCTR2000029591.**

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56 INTRODUCTION

57 Gonorrhoea, caused by *Neisseria gonorrhoeae* (*N. gonorrhoeae*), remains one of the most
58 common sexually transmitted diseases (STDs) worldwide. According to the most recent
59 World Health Organization (WHO) report in 2016, there were 86.9 million incident cases (15-
60 49 years of age) globally, which were more than 10% higher than that in 2012.¹ Left
61 untreated, the infection can cause serious medical problems, particularly for women,
62 including chronic pelvic pain, ectopic pregnancy, and even infertility.² In addition to
63 behavioral interventions to prevent infection of gonorrhoea, timely detection of the infection
64 followed by effective treatment with antibiotics remains the mainstream strategy to control
65 this infection. Unfortunately, *N. gonorrhoeae* has developed resistance to nearly every
66 antibiotic ever used to effectively treat it since sulphonamides were introduced as the first
67 drugs for this treatment in 1940s.³ Due to widespread emergence of the resistant strains, only
68 the extended-spectrum cephalosporin (ESC) and azithromycin which is usually used with
69 ceftriaxone in dual therapy are left to be recommended as first-line regimen for treatment of
70 gonorrhoea in most countries.⁴⁻⁷ However, in recent years, gonococcal strains with reduced
71 susceptibility or resistance to ESC and resistance to high-level azithromycin have been
72 identified from many countries including China⁸⁻⁹. Treatment failures with ceftriaxone have
73 been reported in Japan, Australia, European countries, Canada, and South Africa.¹⁰⁻¹³ Data
74 from the China Gonococcal Resistance Surveillance Programme (China-GRSP) indicated that
75 18.6% of clinical isolates were resistant to azithromycin and 9.7%-12.2% of clinical isolates
76 were less susceptible to ceftriaxone over the years of 2013 and 2016.¹⁴

77 It has been recognized that much of the antimicrobial resistance (AMR) of gonorrhoea
78 originates in Asia and then transmitted to the rest of world.¹⁵⁻¹⁶ Although many factors
79 contribute to the emergence of gonococcal AMR, inappropriate use (misuse or overuse) of
80 antibiotics for treatment of gonorrhoea in clinical practice in many countries in Asia may be
81 one of drivers for AMR due to antibiotic selective pressure. A recent study in China indicated
82 less than 1% of patients with uncomplicated gonorrhoea were treated following the ceftriaxone
83 regimen recommended by the national guidelines (ceftriaxone 250 mg intramuscular as a
84 single dose).¹⁷ More than 70% of the patients received a dosage of more than 1g for their
85 treatment.¹⁷ Several factors affect physicians' prescribing behaviors, including knowledge

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4 86 about the antibiotics, awareness of national guidelines, previous experience in treatment, and
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6 87 trust to the antibiotics. A nationwide survey in China revealed a higher adherence to the
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8 88 national guidelines for treatment of uncomplicated gonorrhoea among physicians who were
9
10 89 aware of the guidelines than those who were not. Additionally, participation in training
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12 90 courses did not significantly improve the prescribing behaviors of physicians,¹⁸ indicating that
13
14 91 more innovative interventions are needed to address the issues of inappropriate antibiotic use
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16 92 in treatment of gonorrhoea in China. Exploring innovative strategies to ensure appropriate use
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18 93 of antibiotics for treatment of gonorrhoea has been listed as one of the priorities in a
19
20 94 comprehensive research plan called ROADMAP (Resistance surveillance, Outcomes due to
21
22 95 AMR, Antibiotic stewardship and application, Diagnostic tools, Mechanisms of AMR,
23
24 96 Antimicrobial assessment, and Population pharmacokinetics and pharmacodynamics) to
25
26 97 address research needs for gonococcal AMR in China.¹⁹

27 98 Mobile health (mHealth), defined as interventions and programmes designed to support
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29 99 medical and public health through the use of mobile technology, has been used as a tool to
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31 100 deliver continuous training and education to healthcare providers.²⁰⁻²¹ Previous randomized
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33 101 controlled trials (RCTs) have shown success of mHealth in optimizing antibiotic
34
35 102 prescribing.²²⁻²⁴ However, there has been no studies to shine a light on whether such training
36
37 103 programme is beneficial to improve antibiotic prescribing behaviors among physicians who
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39 104 provide treatment to patients with STDs. For this purpose, we will conduct a cluster
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41 105 randomized trial to evaluate whether the proposed intervention (online video-based training
42
43 106 programme) could significantly improve physicians' prescribing behaviors to adhere to the
44
45 107 regimens for treatment of uncomplicated gonorrhoea (1g intramuscular ceftriaxone single
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47 108 dose) recommended by the National STD Treatment Guidelines²⁵ (hereinafter referred to the
48
49 109 National Guidelines). Our secondary objective is to understand the reasons of physicians'
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51 110 nonadherence to the online video-based training programme.

52 111 **METHODS AND ANALYSIS**

53 112 **Study design and setting**

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56 113 We will use a parallel-group, cluster randomized controlled trial with one intervention and
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58 114 one control arm, using a 1:1 allocation ratio, to evaluate whether the intervention is superior
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60 115 to the control treatment (**Figure 1**). Selection of provinces for the study is based on the

116 reported incidence of gonorrhoea in 2018. The eight provinces (Jiangsu, Shanghai, Zhejiang,
117 Fujian, Guangdong, Guangxi, Hainan and Yunnan) with the highest incidence of reported
118 gonorrhoea cases (**Figure 2**) in China were selected. Among the eight selected provinces,
119 Jiangsu, Shanghai, Zhejiang, Fujian, Guangdong and Hainan are in the eastern areas, while
120 Guangxi and Yunnan are in the western areas of China. According to geographic location and
121 level of economic development, mainland China was classified into three areas -- Eastern
122 areas (high level of economic development), Middle areas (middle level of economic
123 development) and Western areas (low level of economic development). In China, healthcare
124 workers (especially highly educated physicians) usually prefer to work in more economically
125 developed areas, which results in a severe inequality in the quantity and quality of healthcare
126 workforce. Training is considered an important way to enhance professional skills of
127 healthcare workers, but the effects of training may vary from area to area. Therefore, by
128 evaluating the intervention effects in Chinese hospitals in multiple provinces, the current
129 study may provide insights on whether the intervention can be effective across different local
130 contexts.

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

141 The study will be divided into two sub-trials, i.e., a pilot trial and a main trial. The pilot
142 trial will be conducted in one province randomly selected from the eight study provinces.
143 Data will be collected simultaneously in nine intervention and nine control hospitals for a
144 month to examine the feasibility and acceptability of the intervention. If more than 60% of
145 physicians are willing to use the on-line training, the internal pilot hospitals and their outcome

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4 146 data will then become part of the main trial, and will be followed up for another 5 months
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6 147 (**Figure 1**). The remaining hospitals will be enrolled into the main trial and followed up for 6
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8 148 months (in other words, data collection in the pilot and main trial hospitals will finish at
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10 149 different times). An independent advisory group consisting of key investigators, a programme
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12 150 manager, hospital representatives and a statistician will be established to oversee the trial
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14 151 implementation, review the study progress and provide the corresponding advices.

152 **Participants, recruitment and consent**

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

159 City-level hospitals with highest volume of reported gonorrhoea cases are eligible to
160 participate in the study. Our investigators will prepare a list of eligible hospitals to invite to
161 participate in each of the eight study provinces. The objectives and processes of the study will
162 be explained to the hospital administrations and the in-hospital project coordinators. If a
163 hospital agrees to participate in the study, the in-hospital project coordinator will work
164 together with the study investigators to invite physicians to participate in the study.

165 Physicians who work in the outpatient departments of dermatology (dermatovenerology),
166 urology, andrology or gynaecology and provide informed consent (**see Supplement 1**) will be
167 eligible to participate in the study. Prescriptions of these physicians for treatment of
168 uncomplicated gonorrhoea will be evaluated for their adherence to the National Guidelines.
169 Prescriptions will be excluded from data analysis if they are prescribed to the patients who
170 meet any of the following criteria: (1) younger than 18 years; (2) being pregnant or lactating
171 woman; (3) being allergic to cephalosporin or penicillin or having contraindication to
172 cephalosporin ; (4) being treated with antibiotics for other infections; or (5) have been
173 diagnosed as complicated gonorrhoea, such as disseminated gonococcal infection and pelvic
174 inflammatory disease (PID).

175 **Intervention and control**

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4 176 The proposed intervention to be evaluated in the study is aimed to improve the physicians'
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6 177 adherence to the National Guidelines by reducing inappropriate antibiotic prescribing for
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8 178 treatment of patients infected with *N. gonorrhoeae*. Our research team have designed an
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10 179 information card (**Figure 3**) to be distributed to all participating physicians in the intervention
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12 180 arm hospitals by surface mail. By scanning a QR code on the information card (**Figure 3**),
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14 181 physicians will have access to an online training video developed on the internet platform of
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16 182 WenJuanXing (<https://www.wjx.cn/>). The video covers the workflows and requirements to
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18 183 manage a patient with uncomplicated gonorrhea, including diagnostic criteria and treatment
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20 184 recommendations in accordance with the National Guidelines, and provides the contact
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22 185 information for inquiry related to the diagnosis and treatment.

23 186 In the intervention arm hospitals, project coordinators will provide a less than 30-minute
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25 187 interactive training session in each of the relevant departments (integrated within monthly
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27 188 department meeting) prior to the intervention to explain the information card and the way to
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29 189 use the QR code for accessing the online training video. The intervention will last for 6
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31 190 months. During the 6 months, the project coordinators will send reminders for the video
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33 191 playback to participating physicians through monthly Wechat messages.

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35 192 The frequency of visiting the online training video from each intervention hospital will
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37 193 be recorded in real-time on the WenJuanXing platform. The project manager will evaluate
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39 194 whether or not the intervention is delivered as intended from the server logs.

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41 195 In hospitals allocated to the control arm, physicians will continue to participate in their
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43 196 training programme if they conventionally do it and to prescribe antibiotics for treatment of
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45 197 gonorrhea cases according to their own knowledge and beliefs.

46 198 **Outcomes**

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48 199 The primary outcome is the proportion of prescriptions adherent to the regimens for treatment
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50 200 of uncomplicated gonorrhea recommended by the National Guidelines at the cluster level,
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52 201 which will be documented at baseline and at final evaluation.

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54 202 The secondary outcome is a physician-level binary indicator of nonadherence (defined as
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56 203 having at least 25% of prescriptions nonadherent to the National Guidelines).

57 204 **Sample size estimation**

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59 205 The minimum sample size for this study was obtained using the formula outlined below.²⁶
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$$c = 1 + (Z_{\alpha/2} + Z_{\beta})^2 [\pi_0(1-\pi_0)/n + \pi_1(1-\pi_1)/n + k^2(\pi_0^2 + \pi_1^2)] / (\pi_0 - \pi_1)^2$$

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: $Z_{\alpha/2} = 1.96$, $Z_{\beta} = 1.28$, $\pi_0 = 37.8\%$ (based on a nationwide survey¹⁸ in China), $\pi_1 = 41.6\%$ (based on a consultation of STD clinical experts and control programmers, a minimum 10% increase in adherence to the National Guidelines is deemed clinically relevant in the intervention arm), $n = 100$ (minimum number of uncomplicated gonorrhea patients per hospital within six months), and $k = 0.1$ (based on a nationwide survey¹⁸ 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

236 conducted by an independent statistical analysts using a computer program written in R
237 (V.3.5.3).

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

244 **Data collection**

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

249 Prior to implementation of the intervention, we will have a baseline survey to collect
250 background information of the participating hospitals (see **Supplement 2**) and another
251 baseline questionnaire survey to collect background information of the participating
252 physicians (see **Supplement 3**) in both intervention and control groups for evaluating the
253 appropriateness of randomization. A specific questionnaire survey (see **Supplement 4**) will
254 be conducted among the physicians in the intervention hospitals after implementing the
255 intervention to collect data for measuring the secondary outcome.

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

261 **Data analysis**

262 The data analysis methods are described in full detail in the accompanying data collection and
263 analysis plan (see **Supplement 7**) and are, therefore, only outlined in brief here. We will
264 conduct a complete case analysis of outcomes unless there is an indication that data may be
265 missing not at random, in which multilevel multiple imputation methods to deal with

266 missingness will be employed as sensitivity analysis in addition to the complete case
267 analysis.²⁷

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

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

291 **Process evaluation**

292 Process evaluation will be conducted by collecting real-time summary data on access to the
293 intervention (watching the video) from the WenJuanXing platform. Based on the summary
294 data, hospitals with poor access to the intervention will be selected to conduct qualitative
295 interviews of the public health staff, physicians, and administrative staff to discuss the factors

296 related to the poor access at cluster level. The qualitative data will be analyzed using a simple
297 thematic approach.

298 **Patient and public involvement**

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

302 **ETHICS AND DISSEMINATION**

303 The study protocol has been reviewed and approved by the Medical Ethics Committee of the
304 Chinese Academy of Medical Sciences Institute of Dermatology in Nanjing (2020-LS-004).
305 An amendment will be submitted to the Committee for review and approval if any changes
306 are made to the study protocol. All questionnaires, prescription audits and other data sources
307 will be kept securely and available to authorized individuals for data analysis and reporting
308 purposes only. Data will be entered into the database in an anonymized form to ensure
309 confidentiality. Only principal investigator and other authorized personnel will have access to
310 the final study database. The findings of the trial will be disseminated through reports at the
311 national and international conferences, at least two publications in peer-reviewed journals,
312 and provision of evidence for developing the on-the-job training programmes for physicians
313 who provide services to patients with STDs.

315 **Contributors**

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

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327 **Disclaimer**

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

330 **Competing interests**

331 None declared.

332 **Patient consent**

333 Not required.

334 **Ethics approval**

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

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415 Figure Legends

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4 416 **Figure 1.** Flow chart of the cluster randomized controlled trial.

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7 418 **Figure 2.** Reported incidence rate of gonorrhoea in 2018 in 31 provinces, autonomous regions,
8 and municipalities in the mainland of China.

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13 421 **Figure 3.** The information card with a QR code (hosted by WenJuanXing) to be distributed to
14 physicians in the intervention arm hospitals.

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For peer review only

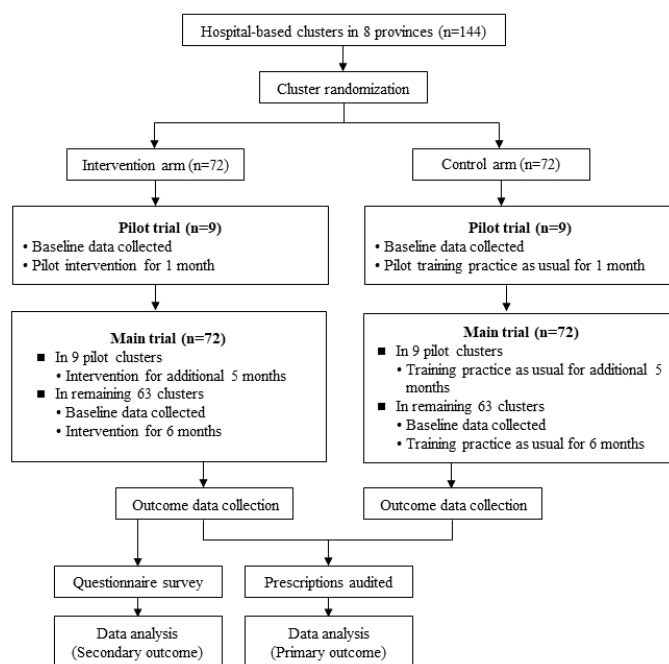


Figure 1

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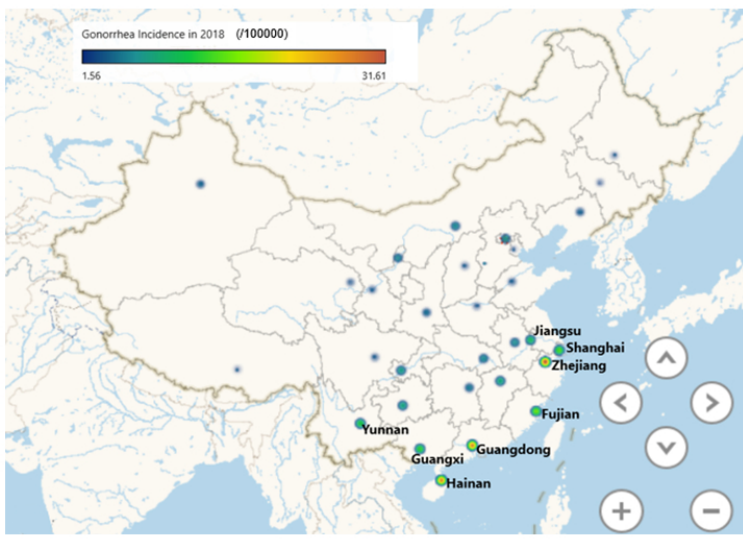


Figure 2

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Gonorrhoea

- 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 gonorrhoea ?

Recommended by
National Center for STD Control, China CDC.
Dermatology and Venereology Branch of Chinese Medical Association.
Dermatology and Venereology Committee of Chinese Preventive Medical Association.
Dermatologists Branch of Chinese Medical Doctor Association.



Please scan QR code @

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 gonorrhoea 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 gonorrhoea 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 gonorrhoea 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?

- 1
2
3 Dermatology & STD
4 Andrology
5 Urology department
6 Obstetrics and gynecology
7 Other (Specific: _____)
8
9
10
11
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13 **7. How long have you been working in this department?**

- 14
15 ≤ 5 years
16 6~10 years
17 ≥ 11 years
18
19
20
21
22

23 **8. Your professional title is:**

- 24 Chief physician
25 Associate chief physician
26 Physician-in-charge
27 Resident physician
28 Other (Specific: _____)
29
30
31
32
33

34 **9. In the last three months, approximately how many cases of uncomplicated gonorrhoea**
35 **have you treated?**

- 36 □□□□ (Number)
37
38
39
40

41 **10. In the last three months, have you received relevant trainings on treatment of**
42 **gonorrhoea?**

- 43 Yes (Specific: _____)
44 No
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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: _____)

1
2
3 **5. The name of hospital you are working at:**
4

- 5 _____(Text)
6
7

8
9 **6. What department do you work in the hospital?**

- 10 Dermatology & STD
11 Andrology
12 Urology department
13 Obstetrics and gynecology
14 Other (Specific: _____)
15
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20
21 **7. How long have you been working in this department?**
22

- 23 ≤ 5 years
24 6~10 years
25 ≥ 11 years
26
27
28
29

30 **8. Your current professional title is:**
31

- 32 Chief physician
33 Associate chief physician
34 Physician-in-charge
35 Resident physician
36 Other (Specific: _____)
37
38
39
40
41

42 **9. In the last three months, approximately how many cases of uncomplicated gonorrhoea**
43 **have you treated?**
44

- 45 _____(Number input) (If answer <1, Skip to End of Survey)
46
47
48

49 **10. Before participating in the on-line video-based training, do you know about the up-**
50 **to-dated National STD Treatment Guidelines for treatment of uncomplicated**
51 **gonorrhoea?**
52

- 53
54 Yes
55 No
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1
2
3 **11. In the last six months, how many times did you access to the on-line training video**
4 **developed on the WenJuanXing platform?**

- 5
6
7 0
8 1~3
9
10 4~6
11 ≥ 7
12

13
14
15 **12. In the last six months, have you received other relevant trainings on treatment of**
16 **gonorrhoea?**

- 17
18
19 Yes (Specific: _____)
20 No
21

22
23
24 **13. What do you think about the up-to-dated regimen in the National STD Treatment**
25 **Guidelines for treatment of uncomplicated gonorrhoea using ceftriaxone 1g as a single**
26 **dose?**

- 27
28
29 Appropriate (enough) dosage
30 Dosage is overdose
31 Dosage is not enough
32 Difference from case to case
33 Don't know
34
35
36

37
38
39 **14. Do you think this on-line video-based training programme is helpful for improving**
40 **your knowledge on management of gonorrhoea?**

- 41
42
43 Very helpful
44 Helpful
45 Not helpful
46 Don't know
47
48
49

50
51 **15. Do you think the participation in this on-line video-based training programme every**
52 **two months occupy too much of your time?**
53
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3 Yes
4 No
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7

8 **16. Will you continue to use this on-line video-based training programme?**
9

- 10 Yes
11 No
12
13
14

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

- 18 Yes
19 No
20
21
22

23 **18. Do you have any suggestions on the on-line training programmes?**
24

- 25 Yes (Specific: _____)
26 No
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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's 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.

- 1
2
3 b) We will define the regimen of 1 g ceftriaxone described by the participating
4 physician for treatment of uncomplicated gonorrhoea as adherence to the
5 National Guidelines (dichotomous outcome).
6
7
8 c) We will estimate the adherence rate and its 95% confidence intervals (CIs)
9 using the total number of eligible prescriptions and the number of the
10 prescriptions met the criteria of adherence.
11
12
13 d) We will estimate the intervention effect which is reported as rate ratio (RR)
14 and 95% CIs compared with the control group. The stratum-specific endline
15 adherence rate ratios will be calculated from the stratum-specific endline
16 adherence rates (mean cluster-level outcomes) in each arm. The crude
17 intervention effect as the overall endline adherence rate ratio between the
18 intervention arm and control arm will be estimated from the weighted
19 average of the stratum-specific endline adherence rate ratios, with weights
20 that are inversely proportional to the stratum-specific variances. Formal
21 testing of the null hypothesis that the overall adherence rate ratio is equal to 1
22 will be conducted using stratified t-test, and 95% confidence interval will be
23 adjusted for between-cluster variance and stratification. To adjust for
24 potentially important covariates, including cluster-level outcome at baseline,
25 and additional patient (age [years], sex [male, female]), linked physician (age
26 [years], sex [male, female], education level [bachelor degree or higher, other],
27 working year [years], department [dermatology or dermatovenerology, other],
28 previous training [yes, no]) and hospital (province located) factors, a two-
29 stage adjusted analyses will be conducted. We will fit a logistic regression
30 model to the individual-level binary outcome data including all covariates of
31 interest as fixed effects, but without adjusting for the treatment effect. The
32 individual-level model predicted values and the individual-level observed
33 values will be used to calculate covariate-adjusted cluster-level ratio
34 residuals. The covariate-adjusted ratio residuals will then be used in place of
35 cluster specific proportions to conduct stratified t-test and calculate 95%
36 confidence interval using the above methods. Statistical significance will be
37 based on the (two-sided) p value estimated for the primary outcome obtained
38 from the covariate-adjusted analyses, considering adjusting increases power
39 and reduces the effect of imbalances between arms with typically minimal
40 risks.
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3 e) We will calculate the differences over 6 months of the intervention in both
4 intervention and control groups, respectively.
5
6 f) We will also conduct subgroup analyses on primary outcome to indicate the
7 intervention effect across the subgroups in terms of hospitals [hospital's
8 level, and category] and physicians [sex, age, education level, working year,
9 department, and previous training]. The same main analysis approach
10 planned above will be used for the cluster-level subgroup analyses to obtain
11 estimates of the treatment effect, its 95% confidence interval and statistical
12 significance within each subgroup. To estimate the statistical significance of
13 any differences in treatment effect among subgroups, analysis of variance
14 will be used on the cluster-level summary outcome data, with terms for
15 treatment, subgroup and the interaction between treatment and subgroup.
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24 **4. How will we measure the barriers to non-adherence to the National** 25 **Guidelines for measuring the secondary outcome?**

- 26
27 a) We will collect the physician's information on socio-demographic
28 characteristics, education background, working experience, and perceptions,
29 attitudes, and practices using a questionnaire survey in the intervention
30 hospitals.
31
32 b) We will define the physicians who have at least 25% prescriptions
33 nonadherent to the National Guidelines as the physician with nonadherence.
34
35 c) We will use the nonadherence as dependent variables for the analyses to
36 identify the factors influencing the nonadherence.
37
38 d) We will present descriptive statistics on the physician's socio-
39 demographic characteristics, education background, working experience,
40 and perceptions, attitudes, and practices.
41
42 e) We will use multivariate logistic regression model to explore the
43 associations between key factors (physician's age [years], education level
44 [bachelor degree or higher, other], working year [years], department
45 [dermatology or dermatovenerology, other], on-line training video access
46 times [≤ 3 , > 3], perceptions on the National Guidelines [appropriate
47 (enough) dosage, other], attitude on the training programme [very helpful or
48 helpful, other]) and the nonadherence. These results will be presented as
49 adjusted odds ratio (AOR), associated 95% CIs and p values. The factors
50 included in the model will be determined theoretically, based on the
51 literature and the findings of our qualitative work.
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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.	<u>Page 8</u>	_____
	WHY		
2.	Describe any rationale, theory, or goal of the elements essential to the intervention.	<u>Page 8</u>	_____
	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).	<u>Page 8</u>	_____
4.	Procedures: Describe each of the procedures, activities, and/or processes used in the intervention, including any enabling or support activities.	<u>Page 8</u>	_____
	WHO PROVIDED		
5.	For each category of intervention provider (e.g. psychologist, nursing assistant), describe their expertise, background and any specific training given.	<u>Page 8</u>	_____
	HOW		

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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.	<u>Page 8</u>	_____
	WHERE		
7.	Describe the type(s) of location(s) where the intervention occurred, including any necessary infrastructure or relevant features.	<u>Page 8</u>	_____
	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.	<u>Page 8</u>	_____
	TAILORING		
9.	If the intervention was planned to be personalised, titrated or adapted, then describe what, why, when, and how.	<u>N/A</u>	_____
	MODIFICATIONS		
10.*	If the intervention was modified during the course of the study, describe the changes (what, when, and how).	<u>N/A</u>	_____
	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.	<u>N/A</u>	_____
12.*	Actual: If intervention adherence or fidelity was assessed, describe the extent to which the intervention was delivered as planned.	<u>Page 8</u>	_____
		<u>N/A</u>	_____

** **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.

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5 † 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
6 published protocol or other published papers (provide citation details) or a website (provide the URL).

7 ‡ If completing the TIDieR checklist for a protocol, these items are not relevant to the protocol and cannot be described until the study is
8 complete.
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11 * We strongly recommend using this checklist in conjunction with the TIDieR guide (see *BMJ* 2014;348:g1687) which contains an explanation
12 and elaboration for each item.

13
14 * The focus of TIDieR is on reporting details of the intervention elements (and where relevant, comparison elements) of a study. Other elements
15 and methodological features of studies are covered by other reporting statements and checklists and have not been duplicated as part of the
16 TIDieR checklist. When a **randomised trial** is being reported, the TIDieR checklist should be used in conjunction with the CONSORT
17 statement (see www.consort-statement.org) as an extension of **Item 5 of the CONSORT 2010 Statement**. When a **clinical trial protocol** is
18 being reported, the TIDieR checklist should be used in conjunction with the SPIRIT statement as an extension of **Item 11 of the SPIRIT 2013**
19 **Statement** (see www.spirit-statement.org). For alternate study designs, TIDieR can be used in conjunction with the appropriate checklist for
20 that study design (see www.equator-network.org).
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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

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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 2a 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

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5		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)
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9		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)
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13		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial
14			8
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16	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
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23	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)
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27	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
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31	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size
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Methods: Assignment of interventions (for controlled trials)

Allocation:

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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

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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
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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”](https://creativecommons.org/licenses/by-nc-nd/3.0/) license.

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