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# BMJ Open

## Optimizing the treatment for uncomplicated acute appendicitis (OPTIMA trial): protocol for a multicentre, randomized double-blinded placebo-controlled study

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Complete List of Authors:	Wu, Jie; The Affiliated BenQ Hospital of Nanjing Medical University, Department of General surgery Jiang, Haiyang; The Affiliated BenQ Hospital of Nanjing Medical University, Department of General surgery Li, Shikuan; The Affiliated Hospital of Qingdao University, Department of Emergency Medicine Wu, Xiuwen; Nanjing Jinling Hospital, Department of Surgery, Jinling Hospital, Nanjing Medical University, Nanjing, Jiangsu Province, China. Wang, Peige; The Affiliated Hospital of Qingdao University, Department of Emergency Medicine Sawyer, Robert; Western Michigan University, General Surgery Department Ren, Jianan; Nanjing Jinling Hospital, Department of Surgery, Jinling Hospital, Nanjing Medical University, Nanjing, Jiangsu Province, China.
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Manuscripts

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3 1 Optimizing the treatment for uncomplicated acute appendicitis (OPTIMA  
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5  
6 2 trial): protocol for a multicentre, randomized double-blinded placebo-  
7  
8  
9 3 controlled study

10  
11 4 Jie Wu<sup>1a</sup>, Haiyang Jiang<sup>1,a</sup>, Shikuan Li<sup>2</sup>, Xiuwen Wu<sup>3</sup>, Peige Wang<sup>2\*</sup>, Robert  
12  
13  
14 5 Sawyer<sup>4\*</sup>, Jianan Ren<sup>3\*</sup>

15  
16 6 1 Department of Surgery, BenQ Medical Centre, The Affiliated BenQ Hospital of Nanjing  
17  
18 7 Medical University, Nanjing, Jiangsu Province, China.

19  
20 8 2 Department of Emergency Medicine, The Affiliated Hospital of Qingdao University

21  
22 9 3 Department of Surgery, Jinling Hospital, Nanjing Medical University, Nanjing, Jiangsu  
23  
24 10 Province, China.

25  
26 11 4 General Surgery Department, Western Michigan University, Kalamazoo, MI, USA.

27  
28  
29 12

30  
31 13 \* Correspondence to:

32  
33 14 Peige Wang, 16 Jiangsu Road, Qingdao, 266000, People's Republic of China. E-mail:  
34  
35 15 wpgzyz@163.com.

36  
37 16 Robert Sawyer, Western Michigan University Homer Stryker MD School of Medicine  
38  
39 17 1000 Oakland Drive, Kalamazoo, MI 49008 USA. E-mail:

40  
41 18 [Robert.Sawyer@med.wmich.edu](mailto:Robert.Sawyer@med.wmich.edu)

42  
43 19 Jianan Ren, Department of Surgery, Jinling Hospital, 305 East Zhongshan Road, Nanjing,  
44  
45 20 210002, China. E-mail: [jiananr@gmail.com](mailto:jiananr@gmail.com)

46  
47 21 Telephone: +8613605169808

48  
49 22 a These authors contributed equally to this work

50  
51 23 Word count:3720

1  
2  
3 **Abstract**  
4

5 **Introduction** Acute appendicitis (AA) is one of the most common surgical  
6  
7  
8 emergencies. An increasing number of studies prove that antibiotics are non-inferior  
9  
10  
11 to appendectomy in patients with uncomplicated AA. Recently, a Korean open-label  
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14 study has been demonstrated that no benefit from antibiotics compared with  
15  
16  
17 symptomatic treatment of uncomplicated AA. Meanwhile, the APPAC III trial has  
18  
19  
20 been conducting to compare the role of antibiotic therapy with placebo in the  
21  
22  
23 treatment CT scan-confirmed uncomplicated AA. The latest guidelines from WSES  
24  
25  
26 recommend antibiotics as a safe alternative to surgery in uncomplicated AA.  
27  
28  
29 However, there is no consensus regarding the optimum regimens, a double-blinded  
30  
31  
32 placebo-controlled study to illustrate the role of antibiotics of uncomplicated AA is  
33  
34  
35 still lacking.  
36

37 **Methods and analysis:** The OPTIMA trial is a multicentre, double-blind, placebo-  
38  
39  
40 controlled, superiority randomized study aiming to evaluate the role of anti-anaerobic  
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42  
43 bacteria antibiotics in the resolution of uncomplicated AA. Patients (aged 18-65  
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45  
46 years) diagnosed with uncomplicated AA (without gangrenous and/or perforated  
47  
48  
49 appendicitis or appendiceal abscess or appendiceal fecalith) are qualified for  
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51  
52 inclusion. Totally, 2400 eligible subjects will participate in the experiment. The  
53  
54  
55 primary endpoint of this study is success rate of the treatment, defined as resolution of  
56  
57  
58 AA resulting in discharge from the hospital without surgical intervention and  
59  
60 recurrent symptoms within 1 year. Secondary endpoints include mortality,  
postintervention complications, recurrent symptoms after treatment up to 1 year,  
hospital stay, sick leave, treatment cost, pain symptom scores, and quality of life. Data  
are reported as number of cases (%), median (range), relative risk, and analyzed using

1  
2  
3 49 Mann Whitney U test, Chi-square test, as appropriate, a P-value < 0.05 is considered  
4  
5 50 significant.

6  
7  
8 51 **Ethics and dissemination:** The protocol has acquired the approve of the Ethics  
9  
10 52 Committee of Jinling Hospital on November 13, 2018(2018NZKY-027-01). The trial  
11  
12 53 findings will be published in peer-reviewed journals.

13  
14 54 **Trial registration:** Chinese Clinical Trial Register, ChiCTR1800018896

### 15 55 **Strengths and limitations of this study**

16  
17  
18 56 Strength 1: To our knowledge, OPTIMA is the first multicentre, randomized, double-  
19  
20 57 blinded, placebo-controlled clinical study comparing ceftazidime combined with  
21  
22 58 ornidazole versus ceftazidime combined with placebo for uncomplicated acute  
23  
24 59 appendicitis to investigate the role of anti-anaerobic drugs in the conservative  
25  
26 60 treatment of appendicitis.

27  
28  
29 61 Strength 2: Multicentre research to ensure that the materials collected are more  
30  
31 62 symbolic. The sub-centers keep the original data, and the data engineers organize and  
32  
33 63 check the data in each center to reduce the errors in the data collection process.

34  
35  
36 64 Strength 3: Ceftazidime and ornidazole are widely used in the treatment of  
37  
38 65 appendicitis due to their low cost and easy availability, which means the optimized  
39  
40 66 non-surgical treatment of appendicitis obtained from the experimental results is easier  
41  
42 67 to popularize.

43  
44  
45 68 Limitation 1: For acute uncomplicated appendicitis, physicians need to make a timely  
46  
47 69 and accurate diagnose and then get informed consent from the patient, to estimate the  
48  
49 70 patients whether meets the uncomplicated diagnosis without surgical pathology  
50  
51 71 remains a challenge for surgeons.

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2  
3 72 Limitation 2: Since the treatment of uncomplicated appendicitis in this study is  
4  
5 73 antibiotics alone, we cannot acquire the results of surgical pathology and  
6  
7 74 bacteriological analysis, only when they need surgical intervention.  
8  
9

10 75

## 11 76 ***Introduction***

12  
13  
14 77 Acute appendicitis (AA) is one of the most common indications for emergency  
15  
16 78 surgery in the world.[1] In 2019, there were an estimated 17.7 million cases  
17  
18 79 (incidence 228/100,000).[2] Appendectomy was first proposed by Mc Burney in  
19  
20 80 1894[3]. For more than a century since then, appendectomy has been the golden  
21  
22 81 standard treatment for appendicitis and has been widely applied in clinical practice.  
23  
24 82 Although appendectomy is generally well tolerated, it is a major surgical intervention  
25  
26 83 and can be associated with postoperative morbidity.  
27  
28  
29

30  
31 84 AA can be classified as either simple or complex. The latter includes  
32  
33 85 gangrenous and/or perforated appendicitis as well as any appendicitis with intra-  
34  
35 86 abdominal or pelvic abscess (IAA).[4] In recent years, the treatment of AA has been  
36  
37 87 under active debate and discourse that an increasing amount of evidence has shown  
38  
39 88 that the majority of patients with uncomplicated acute appendicitis can be treated with  
40  
41 89 antibiotics alone instead of surgery.[5-10] Therefore, the guidelines recommend  
42  
43 90 antibiotic treatment for uncomplicated AA when the patients accept the recurrence  
44  
45 91 risk.[11]  
46  
47  
48

49 92 At present, there is no consensus on the choice of antibiotics and different  
50  
51 93 antibiotic regimens are adopted. A five-year follow-up study of antibiotic therapy for  
52  
53 94 uncomplicated AA from Finland adopted antibiotic therapy with intravenous  
54  
55 95 ertapenem for 3 days followed by 7 days of oral levofloxacin and metronidazole. And  
56  
57 96 the study showed that antibiotic therapy is non-inferior to appendectomy.[8]  
58  
59  
60

1  
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3 97 However, the antibiotics in this trial are not the preferred choice in China. According  
4  
5 98 to our previous study, intravenous three generations of cephalosporins with or without  
6  
7 99 nitroimidazoles are the most common regimens, and the success rate was  
8  
9  
10 100 similar.[12]But the usage of antimicrobial drug regimens in conservative treatment for  
11  
12 101 AA lacks standardization and rationality. Additionally, in other trials or guidelines,  
13  
14 102 the usage of antibiotics regimen is also various, which will bring confusion for  
15  
16 103 physicians in the choice of AA conservative treatment.

17  
18  
19 104 Additionally, some studies have shown no benefit of antibiotic therapy in  
20  
21 105 uncomplicated acute diverticulitis, which results in trials to be designed and  
22  
23 106 conducted aiming to prove the no benefit of antibiotic therapy also in AA. Thus,  
24  
25 107 whether to use antibiotics and which regimen to choose need more clinical trials to  
26  
27 108 prove.

28  
29  
30 109 The APPAC group designed and published a protocol which is a multicentre,  
31  
32 110 double-blind, placebo-controlled, superiority randomized study comparing antibiotic  
33  
34 111 therapy with placebo in the treatment CT scan-confirmed uncomplicated acute  
35  
36 112 appendicitis aiming to evaluate the role of antibiotics in the resolution of  
37  
38 113 uncomplicated acute appendicitis. Recently, Park et al reported results regarding  
39  
40 114 possible spontaneous resolution in uncomplicated acute appendicitis. But their study  
41  
42 115 was single-blind (participants only), not double-blind. Moreover, the recurrence of  
43  
44 116 appendicitis in the no-antibiotic group has a higher tendency than the antibiotic group,  
45  
46 117 although they did not detect statistical differences which maybe because of the small  
47  
48 118 sample size.[13]

49  
50  
51 119 On the other hand, cephalosporins combined with nitroimidazoles as the  
52  
53 120 preoperative prophylactic antibiotic regimens have been proved that this combination  
54  
55 121 can reduce the incidence of surgical site infection compared with cephalosporins  
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1  
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3 122 alone, no matter in non-complicated or complicated AA patients.[14]A prospective  
4  
5 123 randomized double-blinded randomized controlled trial also revealed a significant  
6  
7 124 decrease in wound infection rates by giving 2 postoperative intravenous doses of  
8  
9 125 antibiotics, suggesting postoperative antibiotics are of benefit in simple  
10  
11 126 appendicitis.[15]Accordingly, we inferred that antibiotic regimens have the effects on  
12  
13 127 decreasing recurrence of AA, especially in combination with anti-anaerobes drugs  
14  
15 128 regimens.

16  
17  
18  
19 129 Bacterial resistance has been a global issue. It is increasingly worthwhile to  
20  
21 130 develop rational antibiotic treatment strategies.[16] This study aims to evaluate the  
22  
23 131 therapeutic efficiency of the anti-anaerobes covered strategy as compared to anti-  
24  
25 132 anaerobic uncovered regimens in uncomplicated AA, providing a reference for  
26  
27 133 rational antibiotic selection. To our knowledge, so far, no double-blinded randomized  
28  
29 134 controlled trials are comparing three generations of cephalosporins combined placebo  
30  
31 135 with three generations of cephalosporins combined ornidazole in the treatment of  
32  
33 136 uncomplicated AA.

### 37 **Methods**

#### 38 **Trial design**

39  
40  
41  
42 139 The OPTIMA trial is a multicentre, randomized, double-blind, parallel controlled  
43  
44 140 clinical trial to evaluate the therapeutic qualities and efficiency of a combined anti-  
45  
46 141 anaerobes strategy comparing with no anti-anaerobic agents. In each center, patients  
47  
48 142 are randomly allocated to the experimental treatment arm (intravenously administer  
49  
50 143 ceftazidime combined with ornidazole) or the control arm (intravenously ceftazidime  
51  
52 144 combined with saline simulation agent) in an equal ratio of 1:1. Figure 1 reveals the  
53  
54 145 enrolment, interventions, and follow-up of participants in two conservative treatments  
55  
56 146 for acute appendicitis.  
57  
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2  
3 147 ***Trial setting***  
4

5 148 The trial will take place in 80 hospitals in China. All participating hospitals will  
6  
7  
8 149 recruit a specified number of patients according to the annual admission volume of  
9  
10 150 each center. In all participated hospitals appendectomy is mostly performed  
11  
12 151 laparoscopically.  
13

14  
15 152 ***Eligibility criteria and procedures***  
16

17 153 Patients aged 18 to 65 who are suspected clinical manifestations of acute  
18  
19 154 appendicitis will be allowed to take part in the study. Clinical symptoms, signs, and  
20  
21 155 laboratory tests including blood routine, C reactive protein (CRP), creatinine, and  
22  
23 156 female human chorionic gonadotropin HCG) are evaluated by the surgeon. And  
24  
25 157 patients must have imaging tests to further diagnosis when patients have at least two  
26  
27 158 of the following signs: white blood cell count  $>10 \times 10^9/L$ , axillary temperature  
28  
29 159  $>38.5^\circ\text{C}$ , C reactive protein (CRP) $>10\text{mg/L}$ , acute right lower abdominal pain  
30  
31 160 (including metastatic or persistent right lower abdominal pain), tenderness and  
32  
33 161 rebound pain. If an uncomplicated AA is diagnosed by imaging (ultrasound, CT, or  
34  
35 162 MRI), patients are qualified to be included. Patients or their authorized family  
36  
37 163 members must agree to participate in this study and have signed a written consent  
38  
39 164 form.  
40  
41  
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44

45 165 Exclusion criteria:

- 46  
47 166 1. Exist complications such as abscess, appendiceal fecalith, or perforation  
48  
49 167 2. Appendiceal tumor and/or appendiceal soft tissue mass  
50  
51 168 3. History of acute or chronic appendicitis  
52  
53 169 4. Suspicion of severe sepsis  
54  
55 170 5. Patients with a known history of allergy or other contraindication to the study  
56  
57  
58 171 antibiotics  
59  
60

- 172 6. Patients with pre-existing Immunocompromised
- 173 7. Patients undergoing other antibiotics treatments
- 174 8. Alcoholics
- 175 9. Women who are pregnant or plan to be pregnant or breastfeeding within 3
- 176 months
- 177 10. Refused to sign the informed consent

### 178 ***Allocation and randomisation***

179 Due to differences in the volume of visits from each hospital, the data analyst  
180 will assign a fixed number of cases based on the annual volume of visits to each sub-  
181 center. SAS 9.1 software will be used to realize stratified block randomization.  
182 Stratified randomization process and the results of patient randomization will be  
183 blinded to the researchers. In each center, after signing informed consent, the patients  
184 meeting the trial criteria will be randomly assigned to arm A (ceftazidime combined  
185 with placebo group) or arm B (ceftazidime combined with ornidazole group) in an  
186 equal ratio of 1:1. With the aid of ‘Jinling Rat’ random allocation software, the  
187 patients will achieve their unique study numbers and be grouped randomly and  
188 acquire treatment as designed. Pharmacists get treatment packages from similar  
189 containers which are only distinguishable by a patient's unique identification number.  
190 To ensure patient safety in an emergency, data analysts will provide each hospital  
191 with an emergency unblinding list that contains specific drugs used by patients  
192 participating in the trial. Each hospital should use it only in critical situations, such as  
193 when a patient has severe allergic to the treatment drug of the study.

### 194 ***Blinding***

195 The “Jinling Rat” software is a random allocation tool to maintain the double-  
196 blinded throughout the whole process of the trial. No matter the investigators of

1  
2  
3 197 patients are all not known the treatment packages until finishing the study and the data  
4  
5 198 has been locked.

6  
7  
8 199 Follow-up will be conducted by the surgeon at each center either by telephone  
9  
10 200 or outpatient. The surgeon who participated in the follow-up is not aware of the  
11  
12 201 patient's previous antibiotic regimen and only records as required on the follow-up  
13  
14 202 form.

### 17 203 *Sample size calculation*

18  
19 204 Given the results of previous studies that antibiotics have a success rate of about  
20  
21 205 75% in treating uncomplicated appendicitis and the recurrence rate within one year is  
22  
23 206 25-35% and the recurrence rate of antibiotic treatment for appendicitis is highest  
24  
25 207 within three months after discharge,[5, 17-19] we estimate that the success rate of the  
26  
27 208 combination of anti-anaerobic drugs can increase the cure rate from 75% to 80%. In  
28  
29 209 this condition, we calculated that a minimum of 1091 patients required for each group  
30  
31 210 would achieve a power of  $0.8(1-\beta)$  and one-sided significance level ( $\alpha$ ) of 0.025 to  
32  
33 211 conclude the efficacy of the intervention arm is superior to the control arm in the  
34  
35 212 long-terms of cure rate.

36  
37  
38 213 In addition, some relevant studies chose the short-term efficacy as the primary  
39  
40 214 outcome in consideration that AA is an acute phase disease and the antibiotics will not  
41  
42 215 have effects on subjects after drug metabolism. So, they make the response rate after a  
43  
44 216 course of drug therapy be the primary outcome. In this condition, we projected sample  
45  
46 217 size of 564 participants for each group with 90% power at a two-sided alpha level of  
47  
48 218 0.05 using the PASS software (PASS 11, NCSS software, Kaysville, USA) to  
49  
50 219 conclude the efficacy of the intervention arm is superior to the control arm (from 96%  
51  
52 220 to 99%).  
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3 221 Therefore, to be sufficient to analyze both the short- and long-term efficacy of  
4  
5 222 antibiotic therapy, we chose the first algorithm for sample size estimation, and a total  
6  
7  
8 223 of 2400 patients, with an estimated dropout rate of 10% total of patients.  
9

#### 10 224 ***Recruitment plan***

11  
12 225 Recruitment of participants will start in January 2022 and follow-ups should be  
13  
14 226 carried out at the same time. All 2400 patients are expected to be enrolled by the end  
15  
16  
17 227 of 2022.

#### 18 19 228 ***Interventions***

##### 20 21 229 ***Antibiotic use protocol***

22  
23  
24 230 Patients are randomly assigned in an equal ratio of 1:1 to accept either the  
25  
26 231 experimental treatment arm (intravenously administer ceftazidime combined with  
27  
28 232 ornidazole) or the control arm (intravenously ceftazidime combined with ornidazole  
29  
30 233 simulation agent). The experimental treatment group: Ceftazidime (2g added to  
31  
32 234 100mL 0.9% NaCl injection for intravenous drip, once/12h) + Ornidazole (1g added  
33  
34 235 to 100mL 0.9% NaCl injection for intravenous drip, once/24h) for 3-5d of routine  
35  
36 236 treatment. The control group: ceftazidime (2g added to 100mL 0.9% NaCl injection  
37  
38 237 for intravenous drip, once/12h) + simulation agent (two doses added to 100mL 0.9%  
39  
40 238 NaCl injection for intravenous drip, once/12h) for 3-5d of routine treatment. In both  
41  
42 239 groups, the maximum extension is not more than 7d depending on the treatment  
43  
44  
45 240 response.  
46  
47

#### 48 49 241 ***Criteria for transferring to other treatment***

50  
51 242 In case of a confirmed source of infection through the drug sensitivity test, it is  
52  
53 243 allowed to adopted appropriate antimicrobial agents. If conservative treatment for 24h  
54  
55 244 is not effective or the patient's condition worsened, the treatment strategies should be  
56  
57  
58 245 switched immediately. When suspected an exacerbation of the infection, or the  
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3 246 occurrence of perforated appendicitis or diffuse peritonitis, patients will undergo an  
4  
5 247 emergency laparoscopic appendectomy and undergo appendiceal histopathology and  
6  
7  
8 248 bacterial culture.

9  
10 249 ***Discharge and follow-up***

11  
12 250 Patients meeting the clinical cure criteria will be discharged, which means the  
13  
14 251 following criteria must be met at the same time: body temperature (underarm)  
15  
16 252 <37.5°C, white blood cell count <10.0×10<sup>9</sup>/L, neutrophil percentage <70%, and no  
17  
18 253 deep tenderness, mass or rebound pain in the right lower abdomen of the subjects  
19  
20 254 during follow-up after the medication. According to the time of conservative  
21  
22 255 treatment, the hospitalization follow-up time is set to 1 week. And the following  
23  
24 256 indicators will be collected on day1,3,5,7: physical examination including Visual  
25  
26 257 Analog Scale (VAS), auxiliary examination, therapeutic effect, surgery status (if any).  
27  
28 258 An outpatient follow-up visit is recommended one week after discharge. Standard  
29  
30 259 follow-up of 2 weeks, 1 month, 3 months, 6 months, and 1 year will be performed by  
31  
32 260 the surgeon either by telephone or in an outpatient setting. For patients treated  
33  
34 261 surgically, follow-up should include the assessment of surgical site infection (SSI) in  
35  
36 262 a month.

37  
38 263 If the patient is treated conservatively or surgically for recurrent appendicitis  
39  
40 264 after discharge, the time and contents of treatment should be recorded.

41  
42 265 ***Preparation before implementation***

43  
44 266 Before the commencement of the clinical trial, training on the trial protocol will  
45  
46 267 be conducted by the head of each trial center to the investigators. Each investigator  
47  
48 268 should understand the content of this clinical trial protocol and master the standard  
49  
50 269 methods of enrollment, recording, and judgment criteria according to Standard  
51  
52 270 Operating Procedure (SOP) and Good Clinical Practice (GCP) guidelines. All  
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2  
3 271 participated surgeons and residents ought to accept standard train about unified  
4  
5 272 assessment methods of classified different types of AA.  
6  
7

8 273 ***Outcome measures***

9  
10 274 ***Primary outcome measure***

11  
12 275 The primary endpoint of this study is to evaluate the efficiency and long-term  
13  
14 276 outcome of ceftazidime combined with ornidazole, compared with ceftazidime  
15  
16 277 combined with placebo. It is hypothesized that ceftazidime combined with ornidazole  
17  
18 278 is superior to ceftazidime combined with placebo and will increase the one-year cure  
19  
20 279 rate. The conservative treatment success is defined without a change of antibiotics  
21  
22 280 protocol, without the need for surgical intervention or recurrence of appendicitis for at  
23  
24 281 least one year.  
25  
26  
27

28 282 ***Secondary outcome measures***

29  
30 283 Secondary endpoints are to evaluate the total length of hospital stay; total  
31  
32 284 expenses during the hospitalization; mortality; duration of antibiotic treatment;  
33  
34 285 complications rate; time to fulfill discharge criteria; Pain score (VAS); the use of  
35  
36 286 analgesics; Quality of life assessment (SF-12); readmission rate; percentage of  
37  
38 287 patients requiring appendectomy during initial antibiotic therapy; the number of days  
39  
40 288 absent. Complications will be classified according to conservative treatment or  
41  
42 289 surgery. The former includes antibiotic-related adverse reactions. The latter mainly  
43  
44 290 includes incidence of surgical site infection (SSI), incisional hernia, anastomotic  
45  
46 291 fistula, abdominal abscess, adhesions. The details of data collection were shown in  
47  
48 292 figure 2.  
49  
50  
51  
52

53 293 ***Management and analysis of data***

54 294 ***Data collection and management***  
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3 295 The data managers of the statistical unit are responsible for the data  
4  
5 296 management. In each sub-center, the complete raw information of patients will be  
6  
7 297 stored in electronic medical records and paper medical records in order to facilitate  
8  
9 298 later review. Baseline demographics, as well as the related variables of antibiotic  
10  
11 299 treatment and surgery, will be recorded independently by two data administrators. All  
12  
13 300 variables that need to be counted are provided in the full study protocol. These  
14  
15 301 variables should be registered in case report forms (CRFs) which will be entered into  
16  
17 302 ResMan, an electronic data collection and management system supported by the  
18  
19 303 Chinese Clinical Trial Registry. Data will be encrypted and can only be processed  
20  
21 304 with the authorization of the data managers. A Detail Response Questionnaire (DRQ)  
22  
23 305 will be used by the data managers to recorded missing and wrong data. And then the  
24  
25 306 investigator will check the raw materials kept by the hospital.

### 307 *Statistical analysis*

308 The analysis of primary measures will be based on the intention-to-treat (ITT)  
309 set, and secondary outcomes will be analyzed on the Per-protocol (PP) set. The safety  
310 analysis will be performed on the safety set. When ITT is used for analysis, missing  
311 results will be filled by statistical models based on their data distribution type. The  
312 sets are defined as follows:

- 313 1. ITT set: This set consists of all randomized subjects who have used the study  
314 drug at least once, and have at least one post-drug efficacy evaluation.
- 315 2. PP set: This set includes all randomized subjects who complete all follow-ups  
316 as required by the protocol, have no major protocol violation, and have good  
317 compliance (medication compliance between 80%-120%).
- 318 3. Safety set: This set refers to all the cases that entered the study, used the study  
319 drug at least once, and evaluated the safety after the medication.

1  
2  
3 320 All statistical analyses are performed by SAS 9.1 system programming. All  
4  
5 321 statistical tests, except for the superiority test (a one-sided test) of the primary  
6  
7 322 measures, are conducted on a bilateral basis. Continuous variables are described by  
8  
9 323 mean, standard deviation, median, and upper and lower quartiles. Categorical  
10  
11 324 variables are described by frequency and proportion. The one-sided 97.5% CI for  
12  
13 325 proportion difference will be calculated to evaluate the treatment difference (one-  
14  
15 326 sided test at  $\alpha=0.025$ ). The secondary outcomes will be analyzed using different  
16  
17 327 statistical methods according to the types of data. The t-test or Wilcoxon rank sum  
18  
19 328 test is usually used to compare continuous variables between two groups, and the Chi-  
20  
21 329 square test or Fisher's exact probability test is usually used to compare categorical  
22  
23 330 variables. P-values less than 0.05 will be considered statistically significant for all  
24  
25 331 secondary outcome analyses.

### 30 332 ***Safety and data monitoring***

31  
32  
33 333 The statisticians in charge of randomization are responsible for the unblinding of  
34  
35 334 information when subjects need to know the specific drugs to be used in case of  
36  
37 335 emergency. In case of adverse events, the observing physician can decide whether to  
38  
39 336 terminate the observation based on the condition of the disease.

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41  
42 337 Regular on-site monitoring visits to the trial hospital will be conducted by  
43  
44 338 designated personnel to ensure that all aspects of the clinical trial protocol are strictly  
45  
46 339 followed and the source data will be checked to ensure conformance with the CRFs.  
47  
48 340 At the same time, the principal investigators and the heads of statistical analysis units  
49  
50 341 will group a data management review committee (DMRC). Before the end of the  
51  
52 342 follow-up and data locking, meetings must be held to review suspicious data and/or  
53  
54 343 the relationship between adverse events and drugs one by one.

### 55 344 ***Ethics and dissemination***



1  
2  
3 345 ***Ethics***  
4

5 346 The protocol has acquired the approval of the Ethics Committee of Jinling  
6  
7 347 Hospital on November 13, 2018(2018NZKY-027-01). This trial will be conducted  
8  
9  
10 348 following the Helsinki Declaration and the relevant Chinese clinical trial research  
11  
12 349 norms and regulations.  
13

14  
15 350 ***Patient and Public Involvement***  
16

17 351 Patients or the public were not involved in the design, or conduct, or reporting,  
18  
19 352 or dissemination plans of our research  
20

21 353 ***Protection of the rights and interests of patients***  
22

23  
24 354 Before the start of this trial, research physicians should inform patients of the  
25  
26 355 trial details in writing, such as the nature of the clinical trial, the purpose of the trial,  
27  
28 356 the expected benefits and the risks. Meanwhile, researchers are responsible to protect  
29  
30 357 the privacy of participated patients. Despite they decide to withdraw from the trial at  
31  
32 358 any stage, their medical benefits and rights will not be affected in any way, and they  
33  
34 359 can continue to receive other effective treatment. For possible adverse events, the  
35  
36 360 experiment also set up corresponding solutions. In addition, after the experiment  
37  
38 361 completed, the patients are given the results by telephone.  
39

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42 362 ***Dissemination plan***  
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44 363 The trial findings will be published in peer-reviewed journals and will also be  
45  
46 364 disseminated through presentations at national and/or international conferences.  
47  
48

49 365 ***Discussion***  
50

51 366 The optimization of non-operative management of appendicitis is under active  
52  
53 367 research including the dosage form and duration of antibiotics use.[19, 20] However,  
54  
55 368 the types of antibiotics used in studies are various and the antibiotics they chose are  
56  
57 369 not common in most areas worldwide, like low and middle developing countries. In  
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3 370 addition, the role of anti-anaerobic agents in the treatment of uncomplicated  
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5 371 appendicitis remains to be explored and emphasized. These make it difficult for  
6  
7  
8 372 clinicians to choose a reasonable antibiotic regimen for the treatment of appendicitis.  
9

10 373 According to our previous retrospective study, cephalosporin alone and  
11  
12 374 cephalosporin combined with nitroimidazole are common clinical treatment protocols  
13  
14 375 in China and had similar short-term outcomes in the treatment of uncomplicated AA.  
15  
16 376 However, there are few studies comparing the long-term outcomes of the different  
17  
18 377 treatment strategies due to the lack of follow-up information after discharge.[12] To  
19  
20 378 our knowledge, so far, no double-blinded randomized controlled trials are comparing  
21  
22 379 three generations of cephalosporins combined simulation with three generations of  
23  
24 380 cephalosporins combined ornidazole in the treatment of uncomplicated AA. Thus, we  
25  
26 381 design the OPTIMA trial to evaluate the safety and efficacy of combined anti-  
27  
28 382 anaerobic agents in the treatment and prognostic impact of uncomplicated AA. The  
29  
30 383 results of this study are of great significance for guiding clinical antibiotics use in an  
31  
32 384 environment where antibiotic treatment regimens are not standardized and rational.  
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### 38 385 ***Strengths and limitations of this study***

39  
40 386 In this trial, ultrasound, CT and MRI are all choosing as examination techniques  
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42 387 for appendicitis, since the accurate distinction between complicated and  
43  
44 388 uncomplicated AA is the key to rational treatment of appendicitis. Considering that  
45  
46 389 CT is not available at night in several non-teaching hospitals, and patients with milder  
47  
48 390 conditions may be reluctant to undergo more expensive CT and MRI scans. If we  
49  
50 391 exclude these patients, it might increase the selective bias of the trial due to economic  
51  
52 392 and time factors. Additionally, several studies have demonstrated the usefulness of  
53  
54 393 ultrasound and Alvarado scoring systems in diagnosing appendicitis in recent  
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56 394 years.[21-24] The overall sensitivity and specificity of ultrasound is 76% and 95%,  
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3 395 for CT is 99% and 84% respectively, and MRI is at least as sensitive and specific as  
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5 396 CT.[25-27]Moreover, all examination items and results will be stored timely in the  
6  
7 397 ResMan system, the data will be checked and re-evaluated anytime by the dedicated  
8  
9 398 data management review committee (DMRC) and the patients who do not meet the  
10  
11 399 criteria for uncomplicated appendicitis will be excluded. Thus, the diagnosis of non-  
12  
13 400 complicated AA in this trial is ensured to be reliable.  
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16  
17 401 In terms of antibiotics selection, ertapenem is a broad-spectrum antibiotic with  
18  
19 402 anti-anaerobic effect that has been shown to be effective in the treatment of  
20  
21 403 appendicitis in previous studies and is recommended in the guidelines.[11]However,  
22  
23 404 compared with ertapenem which is expensive and difficult to obtain, the antibiotics  
24  
25 405 chose in this study are readily available and safe, which makes the optimized non-  
26  
27 406 operative treatment of appendicitis obtained from the experimental results is easier to  
28  
29 407 popularize. In addition, according to the previous studies, antibiotic treatment for  
30  
31 408 uncomplicated acute appendicitis had the highest recurrence rate during the first three  
32  
33 409 months after discharge.[5, 19] We speculated that it is related to anaerobic bacteria in  
34  
35 410 the intestinal tract. Thus, we plan to test this by comparing ceftazidime plus  
36  
37 411 simulation with ceftazidime plus ornidazole for uncomplicated AA because of the  
38  
39 412 excellent anti-anaerobic activity of nitroimidazoles.  
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44  
45 413 Up to now, this study is the largest sample size in uncomplicated AA studies, so  
46  
47 414 to be able to evaluate the short-term and long-term prognosis. This study not only  
48  
49 415 discussed the efficacy of combined anti-anaerobic drugs in the treatment of  
50  
51 416 uncomplicated appendicitis but also focused on the cure rate and recurrence rate of  
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53 417 patients in the follow-up after discharge and explored the methods to reduce the  
54  
55 418 recurrence rate of appendicitis.  
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3 419 For uncomplicated AA, it's difficult to get bacteriological evidence from the  
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5 420 patient's abdominal cavity. Therefore, the anti-anaerobic drugs are selected based on a  
6  
7 421 2016 study of clinical characteristics and antimicrobial patterns in complicated intra-  
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9 422 abdominal infections in China. In addition, a 2017 retrospective study of appendicitis  
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11 423 treatment reached similar conclusions about antibiotic use.[28] Besides, a sufficiently  
12  
13 424 large sample and one year of standardized follow-up are required to investigate the  
14  
15 425 effect of anti-anaerobic drugs on the long-term outcome of appendicitis. This is a  
16  
17 426 challenge for the sub-centers in how to conduct research operations in an emergency  
18  
19 427 department setting and how to respond promptly and accurately to emergent  
20  
21 428 problems.

## 26 429 **Conclusion**

28 430 The OPTIMA trial is a multicentre, double-blind, placebo-controlled, superiority  
29  
30 431 randomized study aiming to evaluate the role of anti-anaerobic bacteria antibiotics in  
31  
32 432 the resolution of uncomplicated AA.  
33  
34

35 433

## 37 434 **Declarations**

39 435 **Acknowledgements:** We acknowledge Jingdong Junzhuo Pharmaceutical Co., LTD  
40  
41 436 for providing the study drugs.

42 437 **Authors' contributions:** All authors were involved in the study design, and read and  
43  
44 438 approved the final manuscript.

45 439 **Competing interests:** Jingdong Junzhuo Pharmaceutical Co., LTD provides the  
46  
47 440 study drugs (ornidazole and sodium chloride injection, ceftazidime injection and  
48  
49 441 simulants) for this investigator-initiated study but has no influence on the study  
50  
51 442 design, data analysis, or report. The investigators take full responsibility for the  
52  
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3 443 integrity and content of this paper. And the authors declare that they have no  
4  
5 444 competing interests.

6  
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8  
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10  
11 447 and TGKS2019002).

12  
13  
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23  
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### 532 **Figure legends**

533 Figure 1: OPTIMA flowchart of enrollment, interventions, and follow-up.

534 Abbreviation: ivgtt, intravenous drip; CRP, C reactive protein; VAS, Visual Analog  
535 Scale.

536 Figure 2: Follow-up schedule of OPTIMA. Abbreviation: VAS, Visual Analog Scale.

537 \* Follow-up after discharge can be conducted either by telephone or in an outpatient  
538 clinic as recommended.

539 \*\* If symptoms of suspected appendicitis appear during follow-up after discharge,  
540 relevant examinations should be performed and records should be made.

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3 541 \*\*\* Patients undergoing surgical treatment should be recorded separately including  
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5 542 disease complications and surgical complications as well as their respective adverse  
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8 543 events.  
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For peer review only



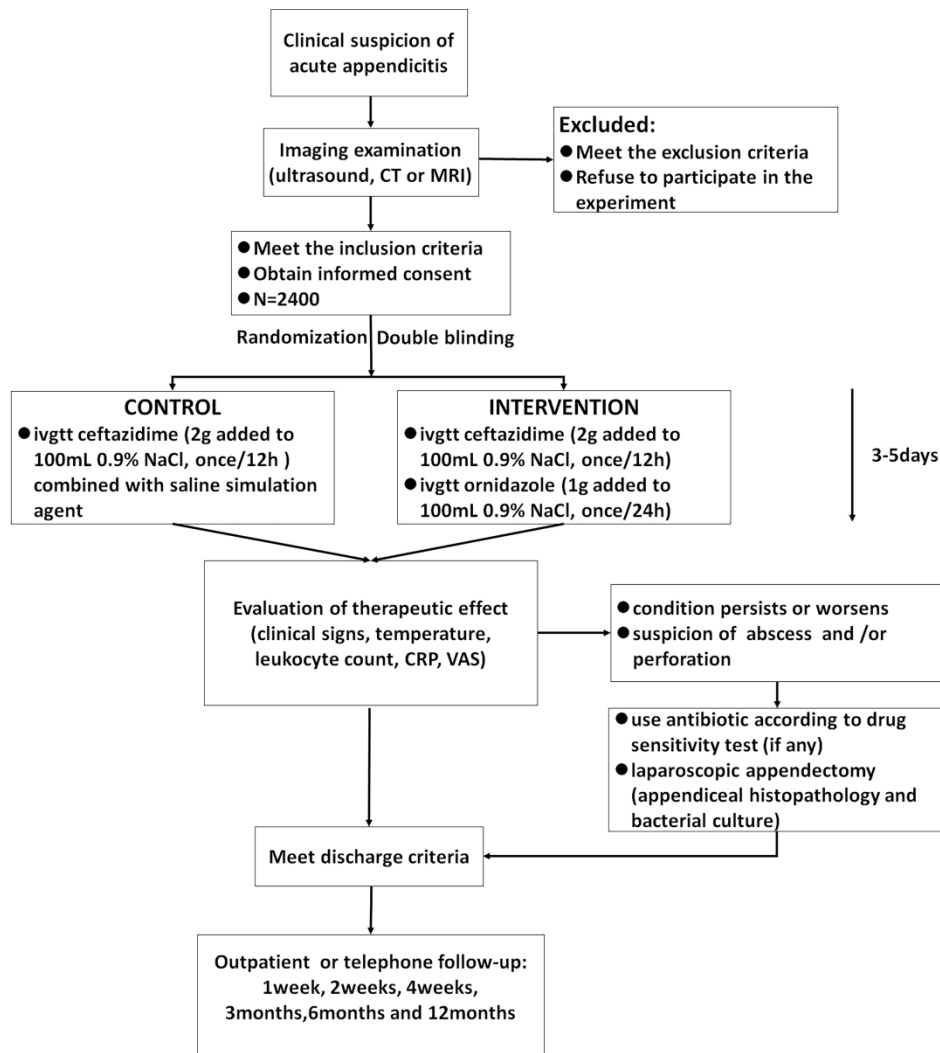


Figure 1: OPTIMA flowchart of enrollment, interventions, and follow-up. Abbreviation: ivgtt, intravenous drip; CRP, C reactive protein; VAS, Visual Analog Scale.

312x326mm (300 x 300 DPI)

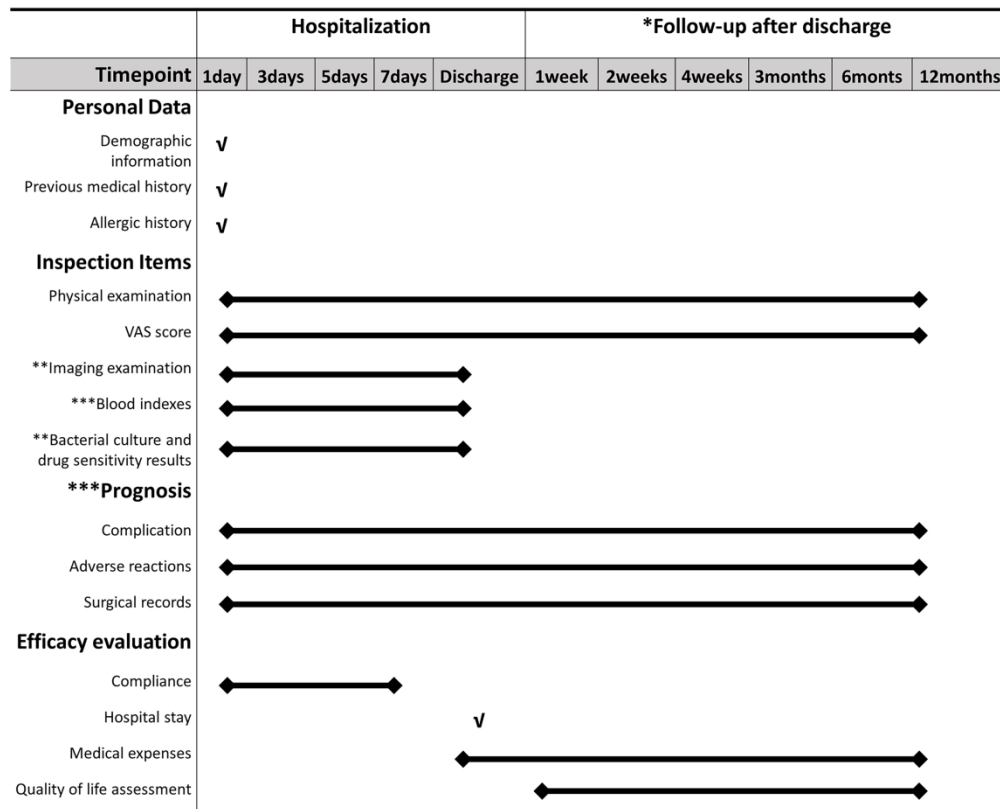


Figure 2: Follow-up schedule of OPTIMA. Abbreviation: VAS, Visual Analog Scale.

\* Follow-up after discharge can be conducted either by telephone or in an outpatient clinic as recommended.

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\*\*\* Patients undergoing surgical treatment should be recorded separately including disease complications and surgical complications as well as their respective adverse events.

328x265mm (300 x 300 DPI)



STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description	Addressed on page number
<b>Administrative information</b>			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	P1/L1-3
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	P3/L53
	2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	3	Date and version identifier	
Funding	4	Sources and types of financial, material, and other support	P18/L437-444
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	P1/L4-L22
	5b	Name and contact information for the trial sponsor	P1/L13-20
	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	P18/L439
	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)	P14/L339-340

## 1 Introduction

2				
3	Background and	6a	Description of research question and justification for undertaking the trial, including summary of relevant	P4/L76-135
4	rationale		studies (published and unpublished) examining benefits and harms for each intervention	
5				
6		6b	Explanation for choice of comparators	P6/L128-135
7				
8	Objectives	7	Specific objectives or hypotheses	P6/L125-127
9				
10	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group),	
11			allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	P6/L138-140
12				
13				
14	<b>Methods: Participants, interventions, and outcomes</b>			
15				
16	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will	P6/L147
17			be collected. Reference to where list of study sites can be obtained	
18				
19	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and	P7/L152-176
20			individuals who will perform the interventions (eg, surgeons, psychotherapists)	P11/L265-271
21				
22	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be	P10/L228-239
23			administered	
24		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose	P10/L241-247
25			change in response to harms, participant request, or improving/worsening disease)	
26		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence	P11/L254-259
27			(eg, drug tablet return, laboratory tests)	
28		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	P10/L229-232
29				
30	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood	P12/L274-290
31			pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg,	
32			median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen	
33			efficacy and harm outcomes is strongly recommended	
34	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for	P6/L138-145
35			participants. A schematic diagram is highly recommended (see Figure)	
36				
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1	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	P9/L203-222
2				
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4	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	P10/L224-226
5				
6				
7	<b>Methods: Assignment of interventions (for controlled trials)</b>			
8	Allocation:			
9				
10	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	P8/L178-192
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16	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	P8/L194-201
17				
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20	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	P8/L178
21				
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24	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	P8/L182,195-201
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27		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	P14/L332-335
28				
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31	<b>Methods: Data collection, management, and analysis</b>			
32				
33	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	P11/L253-261
34				
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39		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	P11/L254-255, L258
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1	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	P14/L336-342
2				
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5	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	P13/319-330
6				
7				
8		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	P13/L312-318
9				
10		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	P13/L307-310
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14	<b>Methods: Monitoring</b>			
15				
16	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	P14/L339-340
17				
18				
19				
20				
21				
22		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	
23				
24				
25	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	P12/L287-290
26				
27				
28	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	P14/L340-342
29				
30				
31				
32	<b>Ethics and dissemination</b>			
33				
34	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	P14/L345-346
35				
36				
37	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)	Not applicable
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1	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	P7/L161-163
2				
3				
4		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Detail in informed consent form
5				
6				
7				
8	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	Detail in informed consent form
9				
10				
11				
12				
13	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	P18/L440-441
14				
15				
16	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	P18/L445-450
17				
18				
19	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	Detail in informed consent form
20				
21				
22				
23				
24	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, health care professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	P15/L362-363
25				
26				
27				
28		31b	Authorship eligibility guidelines and any intended use of professional writers	Not applicable
29				
30		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Not applicable
31				
32				
33	<b>Appendices</b>			
34	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	See supplement materials
35				
36				
37				
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39	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	Not applicable
40				
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1 \*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.  
2 Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons  
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# BMJ Open

## Optimizing the treatment for uncomplicated acute appendicitis (OPTIMA trial): A protocol for a multicenter, randomized double-blinded placebo-controlled study

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Complete List of Authors:	Wu, Jie; The Affiliated BenQ Hospital of Nanjing Medical University, Department of General surgery Jiang, Haiyang; The Affiliated BenQ Hospital of Nanjing Medical University, Department of General surgery Li, Shikuan; The Affiliated Hospital of Qingdao University, Department of Emergency Medicine Wu, Xiuwen; Nanjing Jinling Hospital, Department of Surgery, Jinling Hospital, Nanjing Medical University, Nanjing, Jiangsu Province, China. Wang, Peige; The Affiliated Hospital of Qingdao University, Department of Emergency Medicine Sawyer, Robert; Western Michigan University, General Surgery Department Ren, Jianan; Nanjing Jinling Hospital, Department of Surgery, Jinling Hospital, Nanjing Medical University, Nanjing, Jiangsu Province, China.
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Manuscripts

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3 1 Optimizing the treatment for uncomplicated acute appendicitis (OPTIMA  
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6 2 trial): A protocol for a multicenter, randomized double-blinded placebo-  
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9 3 controlled study

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11 4 Jie Wu<sup>1a</sup>, Haiyang Jiang<sup>1,a</sup>, Shikuan Li<sup>2</sup>, Xiuwen Wu<sup>3</sup>, Peige Wang<sup>2\*</sup>, Robert  
12  
13  
14 5 Sawyer<sup>4\*</sup>, Jianan Ren<sup>3\*</sup>

15  
16 6 1 Department of Surgery, BenQ Medical Centre, The Affiliated BenQ Hospital of Nanjing  
17  
18 7 Medical University, Nanjing, Jiangsu Province, China.

19  
20 8 2 Department of Emergency Medicine, The Affiliated Hospital of Qingdao University

21  
22 9 3 Department of Surgery, Jinling Hospital, Nanjing Medical University, Nanjing, Jiangsu  
23  
24 10 Province, China.

25  
26 11 4 General Surgery Department, Western Michigan University, Kalamazoo, MI, USA.

27  
28  
29 12

30  
31 13 \* Correspondence to:

32  
33 14 Peige Wang, 16 Jiangsu Road, Qingdao, 266000, People's Republic of China. E-mail:  
34  
35 15 wpgzyz@163.com.

36  
37 16 Robert Sawyer, Western Michigan University Homer Stryker MD School of Medicine  
38  
39 17 1000 Oakland Drive, Kalamazoo, MI 49008 USA. E-mail:

40  
41 18 [Robert.Sawyer@med.wmich.edu](mailto:Robert.Sawyer@med.wmich.edu)

42  
43 19 Jianan Ren, Department of Surgery, Jinling Hospital, 305 East Zhongshan Road, Nanjing,  
44  
45 20 210002, China. E-mail: [jiananr@gmail.com](mailto:jiananr@gmail.com)

46  
47 21 Telephone: +8613605169808

48  
49 22 a These authors contributed equally to this work

50  
51 23 Word count:3882

1  
2  
3 **Abstract**  
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5 **Introduction** Emerging evidence has shown that an antibiotics-first strategy is a  
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26 **Introduction** Emerging evidence has shown that an antibiotics-first strategy is a  
27 viable treatment option for uncomplicated acute appendicitis (AA). Although there  
28 has recently been an interest and increase in the use of antibiotics as the primary  
29 strategy for treating uncomplicated AA, there is no consensus regarding the optimum  
30 antibiotic regimen. In particular, the long-term outcomes of different antibiotic  
31 regimens, such as the recurrence rate, still lack evidence. Given that the flora of the  
32 appendix is mainly anaerobic bacteria and that a Korean open-label study showed a  
33 higher proportion of recurrence in the symptomatic treatment group than antibiotic  
34 group, we hypothesized that anti-anaerobe regimens could decrease the recurrence  
35 rate compared to those that did not include anti-anaerobic antibiotics.

36 **Methods and analysis:** The OPTIMA trial is a multicenter, double-blind, placebo-  
37 controlled, superiority randomized study aiming to evaluate the role of anti-anaerobic  
38 antibiotics in the resolution of uncomplicated AA. Patients (18-65years) with  
39 uncomplicated AA (without gangrenous and/or perforated appendicitis or appendiceal  
40 abscess or appendiceal fecaliths) are eligible for inclusion. The primary endpoint of  
41 this study is the success rate of the treatment, defined as the resolution of AA  
42 resulting in discharge from the hospital without surgical intervention and recurrent  
43 symptoms within 1 year. Secondary endpoints include mortality, postintervention  
44 complications, recurrent symptoms up to 1 year after treatment, hospital stay, sick  
45 leave, treatment cost, pain symptom scores, and quality of life. Data are reported as  
46 the number of cases (%), median (range), and relative risk and will be analyzed using  
47 the Mann–Whitney U test or chi-square test, as appropriate, and a P value < 0.05 will  
48 be considered significant.

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2  
3 49 **Ethics and dissemination:** The protocol has acquired the approve of the Ethics  
4  
5 50 Committee of Jinling Hospital on November 13, 2018(2018NZKY-027-01). The trial  
6  
7 51 findings will be published in peer-reviewed journals.

8  
9  
10 52 **Trial registration:** Chinese Clinical Trial Register, ChiCTR1800018896

### 11 53 **Strengths and limitations of this study**

12  
13  
14 54 Strength 1: The OPTIMA trial is the first multicenter, randomized, double-blinded,  
15  
16 55 placebo-controlled clinical study comparing ceftazidime combined with ornidazole  
17  
18 56 versus ceftazidime combined with placebo for uncomplicated acute appendicitis to  
19  
20 57 investigate the role of anti-anaerobic drugs in the conservative treatment of  
21  
22 58 appendicitis.

23  
24  
25  
26 59 Strength 2: A double-blinded trial with a placebo can reduce bias and confirm the role  
27  
28 60 of anti-anaerobic agents in the treatment of appendicitis.

29  
30  
31 61 Strength 3: The data will be collected and saved in an electronic data capture system  
32  
33 62 (EDC) to guarantee the integrity of the data, and the data engineers will organize and  
34  
35 63 check the data from each center to reduce errors in the data collection process.

36  
37  
38 64 Limitation 1: Since the treatment of uncomplicated appendicitis in this study involves  
39  
40 65 antibiotics alone, we cannot collect data on surgical pathology and bacteriological  
41  
42 66 analysis, unless surgical intervention is required.

43  
44  
45 67

### 46 68 **Introduction**

47  
48  
49 69 Acute appendicitis (AA) is one of the most common indications for emergency  
50  
51 70 surgery worldwide.[1] In 2019, there were an estimated 17.7 million cases (incidence,  
52  
53 71 228/100,000).[2] Appendectomy was first proposed by Mc Burney in 1894.[3] For  
54  
55 72 more than a century since then, appendectomy has been the gold standard treatment  
56  
57 73 for appendicitis and has been widely applied in clinical practice. However, the  
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3 74 treatment of AA has been under active debate and discourse in recent years, and an  
4  
5 75 increasing amount of evidence has shown that the majority of patients with  
6  
7 76 uncomplicated acute appendicitis can be treated with antibiotics alone instead of  
8  
9  
10 77 surgery.[4-12] Therefore, the guidelines recommend antibiotic treatment for  
11  
12 78 uncomplicated AA when patients accept the recurrence risk.[13]

13  
14  
15 79 At present, there is no consensus on the choice of antibiotics, and various  
16  
17 80 antibiotic regimens have been adopted. Some recent clinical studies have focused on  
18  
19 81 defining a better regimen, including the route of administration, course of treatment  
20  
21 82 and even supportive care without antibiotics.[5, 14-19] A randomized clinical trial on  
22  
23 83 antibiotic therapy for uncomplicated AA from Finland adopted antibiotic therapy with  
24  
25 84 intravenous ertapenem for 3 days followed by 7 days of oral levofloxacin and  
26  
27 85 metronidazole and showed that antibiotic therapy is noninferior to appendectomy.  
28  
29 86 [15] Park et al. performed a single-blinded (participants only) trial and reported  
30  
31 87 results regarding possible spontaneous resolution of uncomplicated acute appendicitis.  
32  
33 88 [16] Recently, the APPAC group designed and published a protocol for a multicenter,  
34  
35 89 double-blinded, placebo-controlled, superiority randomized study comparing  
36  
37 90 antibiotic therapy with placebo for the treatment of CT scan-confirmed uncomplicated  
38  
39 91 acute appendicitis, aiming to evaluate the role of antibiotics in the resolution of  
40  
41 92 uncomplicated acute appendicitis (NCT03234296).

42  
43  
44 93 However, the antibiotics used in these trials are not the preferred choice in most  
45  
46 94 countries, including China. According to our previous study, three generations of  
47  
48 95 intravenously administered cephalosporins with or without nitroimidazoles are the  
49  
50 96 most common regimens, and the usage of antimicrobial drug regimens in conservative  
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52 97 treatment for AA lacks standardization and rationale.[20] Additionally, the usage of  
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3 98 antibiotic regimens in clinical trials or guidelines also varies, which can cause  
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5 99 confusion for physicians regarding the choice of conservative AA treatment.  
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7

8 100 The trial from Park et al. showed a higher tendency of recurrence of appendicitis  
9  
10 101 in the no-antibiotic group than in the antibiotic group, although the authors did not  
11  
12 102 detect significant differences, which may be because of the small sample size.[16] In  
13  
14 103 addition, cephalosporins combined with nitroimidazoles as preoperative prophylactic  
15  
16 104 antibiotic regimens have been proven to reduce the incidence of surgical site infection  
17  
18 105 compared with cephalosporins alone in both noncomplicated and complicated AA  
19  
20 106 patients.[21] A prospective double-blinded randomized controlled trial revealed a  
21  
22 107 significant decrease in wound infection rates with 2 postoperative intravenous doses  
23  
24 108 of antibiotics, suggesting that postoperative antibiotics are of benefit in simple  
25  
26 109 appendicitis.[22] Some etiological studies also suggested that anaerobic bacteria in  
27  
28 110 uncomplicated appendicitis are a nonnegligible risk factor for disease progression.[23,  
29  
30 111 24] Accordingly, we hypothesized that a combination of anti-anaerobe drug regimens  
31  
32 112 would have stronger effects on decreasing the recurrence of AA.  
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38 113 To our knowledge, this double-blinded randomized controlled study is the first to  
39  
40 114 evaluate the therapeutic efficiency (a composite primary outcome including in-  
41  
42 115 hospital cure rate, transfer rate and recurrence rate within a one year follow-up period)  
43  
44 116 of the anti-anaerobe covered strategy compared to anti-anaerobic uncovered regimens  
45  
46 117 in uncomplicated AA, providing a reference for rational antibiotic selection.  
47  
48

## 49 118 **Methods**

### 50 119 **Trial design**

51  
52 120 The OPTIMA trial is a multicenter, randomized, double-blinded, parallel  
53  
54 121 controlled clinical trial designed to evaluate the therapeutic qualities and efficiency of  
55  
56 122 a combination anti-anaerobe strategy compared with no use of anti-anaerobic agents.  
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3 123 At each center, patients are randomly allocated to the experimental treatment arm  
4  
5 124 (intravenously administered ceftazidime combined with ornidazole) or the control arm  
6  
7  
8 125 (intravenously administered ceftazidime combined with a saline simulation agent) in a  
9  
10 126 1:1 ratio. Figure 1 shows the enrollment process, interventions, and follow-up of  
11  
12 127 participants in two conservative treatments for acute appendicitis.

### 128 ***Trial setting***

129 The trial will take place at 80 hospitals in China. All participating hospitals will  
130 recruit a specified number of patients according to the annual admission volume of  
131 each center. At all participating hospitals, appendectomy is usually performed  
132 laparoscopically.

### 133 ***Diagnosis***

134 A rapid and correct diagnosis of uncomplicated appendicitis is the key to the  
135 success of the study. First, imaging has irreplaceable advantages in the diagnosis and  
136 differentiation of uncomplicated appendicitis. Moreover, due to the high sensitivity  
137 and specificity of the appendicitis inflammatory response (AIR) score in the  
138 identification of advanced appendicitis, we combined the AIR score and imaging tests  
139 to diagnose uncomplicated appendicitis.[25-30] All patients with clinically suspected  
140 AA will be enrolled for further screening. Clinical history, physical examination and  
141 laboratory tests, including routine blood tests (white cell count, proportion of  
142 polymorphonuclear leukocytes), C-reactive protein (CRP), creatinine, and female  
143 human chorionic gonadotropin (HCG), will be evaluated by the surgeon. The AIR  
144 score will be recorded according to the inspection results to define three groups: low  
145 probability (<5 points), medium probability (5–8 points), and high probability (>8  
146 points). Then, all patients will undergo imaging.

### 147 ***Inclusion criteria:***

- 1  
2  
3 148 1. Age 18-65 years  
4  
5 149 2. AIR score: low probability (<5 points), medium probability (5–8 points)  
6  
7  
8 150 3. Diagnosis of uncomplicated AA confirmed by imaging (ultrasound, CT or  
9  
10 151 MRI) defined by the following criteria: appendix diameter greater than 6 mm,  
11  
12 152 thickened appendix wall, appendix lumen stenosis, inflammatory edema and a small  
13  
14  
15 153 amount of effusion around the appendix.

16  
17 154 ***Exclusion criteria:***

- 18  
19 155 1. Age <18 or >65  
20  
21 156 2. AIR score >8  
22  
23  
24 157 3. Diagnosis of existing complications by imaging (ultrasound, CT or MRI), such  
25  
26 158 as abscess, appendiceal fecalith, or perforation  
27  
28 159 4. Appendiceal tumor and/or appendiceal soft tissue mass  
29  
30 160 5. History of acute or chronic appendicitis  
31  
32 161 6. Suspicion of severe sepsis  
33  
34 162 7. Patients with a known history of allergies or other contraindications to the  
35  
36 163 study antibiotics  
37  
38 164 8. Immunocompromised patients  
39  
40 165 9. Patients undergoing other antibiotic treatments  
41  
42 166 10. Alcoholics  
43  
44 167 11. Women who are pregnant or plan to become pregnant or who are  
45  
46 168 breastfeeding within 3 months of the study  
47  
48 169 12. Refusal to sign the informed consent  
49  
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51  
52

53 170 ***Allocation and randomisation***

54  
55  
56 171 Due to differences in the volume of visits from each hospital, the data analyst  
57  
58 172 will assign a fixed number of cases to each subcenter based on its annual volume of  
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3 173 visits. SAS 9.1 software will be used to achieve stratified block randomization. The  
4  
5 174 researchers will be blinded to the stratified randomization process and the results of  
6  
7  
8 175 patient randomization. At each center, after signing the informed consent, the patients  
9  
10 176 meeting the trial criteria will be randomly assigned to arm A (ceftazidime combined  
11  
12 177 with placebo group) or arm B (ceftazidime combined with ornidazole group) in a 1:1  
13  
14  
15 178 ratio. Each patient will be given a unique study number, undergo random grouping  
16  
17 179 and be assigned a designated treatment with 'Jinling Rat' random allocation software.  
18  
19 180 The pharmacists will obtain treatment packages in similar containers that are  
20  
21 181 distinguishable only by a patient's unique identification number. To ensure patient  
22  
23  
24 182 safety in an emergency, data analysts will provide each hospital with an emergency  
25  
26 183 unblinding list that includes the specific drugs used by the patients participating in the  
27  
28 184 trial. Each hospital should use it only in critical situations, such as when a patient has  
29  
30 185 severe allergies to the treatment drug in the study.

### 33 186 ***Blinding***

35 187 Jinling Rat software is a random allocation tool used to maintain double  
36  
37 188 blinding throughout the whole process of the trial. The investigators and the patients  
38  
39 189 remain unaware of the treatment packages until the study is finished and the data have  
40  
41 190 been locked.

44 191 Follow-up will be conducted by the surgeon at each center either by telephone  
45  
46 192 or outpatient visits. The surgeon who performs the follow-up is not aware of the  
47  
48 193 patient's previous antibiotic regimen and records only the required information on the  
49  
50 194 follow-up form.

### 54 195 ***Sample size calculation***

56 196 Given the results of previous studies indicating that antibiotics have a success  
57  
58 197 rate of approximately 75% in treating uncomplicated appendicitis, the recurrence rate  
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3 198 within one year is 25-35%, and the recurrence rate with antibiotic treatment for  
4  
5 199 appendicitis is highest within the three months after discharge,[7, 9, 15, 16] we  
6  
7 200 estimate that the success rate of the combination of anti-anaerobic drugs can increase  
8  
9 201 the cure rate from 75% to 80%. Under this condition, we calculated that a minimum  
10  
11 202 of 1091 patients in each group would achieve a power of 0.8 ( $1-\beta$ ) and a one-sided  
12  
13 203 significance level ( $\alpha$ ) of 0.025 to conclude that the efficacy of the intervention arm is  
14  
15 204 superior to that of the control arm regarding the long-term cure rate.  
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19 205 In addition, some relevant studies have chosen short-term efficacy as the primary  
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21 206 outcome considering that AA is an acute phase disease and that antibiotics will not  
22  
23 207 have effects on subjects after drug metabolism. Therefore, those studies have selected  
24  
25 208 the response rate after a course of drug therapy as the primary outcome. Under this  
26  
27 209 condition, we projected a sample size of 564 participants for each group with 90%  
28  
29 210 power at a two-sided alpha level of 0.05 using PASS software (PASS 11, NCSS  
30  
31 211 software, Kaysville, USA) to conclude that the efficacy of the intervention arm is  
32  
33 212 superior to that of the control arm (from 96% to 99%).  
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37 213 Therefore, to sufficiently analyze both the short- and long-term efficacy of  
38  
39 214 antibiotic therapy, we chose the first algorithm for sample size estimation, and a total  
40  
41 215 of 2400 patients will be recruited, given an estimated dropout rate of 10% of all  
42  
43 216 patients.  
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### 47 217 ***Recruitment plan***

48  
49 218 Recruitment of participants will start in January 2022 and follow-ups should be  
50  
51 219 carried out at the same time. All 2400 patients are expected to be enrolled by the end  
52  
53 220 of 2022.  
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### 56 221 ***Interventions***

### 57 222 ***Antibiotic use protocol***

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3 223 Patients will be randomly assigned in a 1:1 ratio to either the experimental  
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5 224 treatment arm (intravenously administered ceftazidime combined with ornidazole) or  
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7  
8 225 the control arm (intravenously administered ceftazidime combined with an ornidazole  
9  
10 226 simulation agent). The experimental treatment group will receive ceftazidime (2 g  
11  
12 227 added to 100 mL 0.9% NaCl injection for intravenous drip, once every 12 h) +  
13  
14  
15 228 ornidazole (1 g added to 100 mL 0.9% NaCl injection for intravenous drip, once every  
16  
17 229 24 h) for 3-5 d of routine treatment. The control group will receive ceftazidime (2 g  
18  
19 230 added to 100 mL 0.9% NaCl injection for intravenous drip, once every 12 h) +  
20  
21 231 simulation agent (two doses added to 100 mL 0.9% NaCl injection for intravenous  
22  
23 232 drip, once every 12 h) for 3-5 d of routine treatment. In both groups, the maximum  
24  
25  
26 233 extension will not be more than 7 d, depending on the treatment response.

#### 27 28 234 ***Criteria for transferring to another treatment***

29  
30 235 In the case of a confirmed source of infection through the drug sensitivity test,  
31  
32 236 appropriate antimicrobial agents can be adopted. If conservative treatment for 24 h is  
33  
34 237 not effective or the patient's condition worsens, the treatment strategies should be  
35  
36 238 switched immediately. When an exacerbation of the infection or the occurrence of  
37  
38 239 perforated appendicitis or diffuse peritonitis is suspected, patients will undergo an  
39  
40 240 emergency laparoscopic appendectomy and appendiceal histopathology and bacterial  
41  
42 241 culture.

#### 43 44 242 ***Discharge and follow-up***

45  
46  
47 243 Patients meeting the clinical cure criteria will be discharged, which means that  
48  
49 244 the following criteria must be met at the same time: body temperature (underarm)  
50  
51 245 <37.5°C, white blood cell count <10.0×10<sup>9</sup>/L, neutrophil percentage <70%, and no  
52  
53 246 deep tenderness, mass or rebound pain in the right lower abdomen of the subjects  
54  
55  
56 247 during follow-up after treatment with the medication. According to the duration of  
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1  
2  
3 248 conservative treatment, the hospitalization follow-up time will be set to 1 week. The  
4  
5 249 following indicators will be collected on days 1, 3, 5, and 7: a physical examination,  
6  
7 250 including the Visual Analog Scale (VAS), auxiliary examination, therapeutic effect,  
8  
9 251 and surgery status (if any). An outpatient follow-up visit is recommended one week  
10  
11 252 after discharge. Standard follow-ups of 2 weeks, 1 month, 3 months, 6 months, and 1  
12  
13 253 year will be performed by the surgeon either by telephone or in an outpatient setting.  
14  
15 254 For patients treated surgically, follow-up should include the assessment of surgical  
16  
17 255 site infection (SSI) in one month.

18  
19 256 If the patient is treated conservatively or surgically for recurrent appendicitis  
20  
21 257 after discharge, the time and components of treatment should be recorded.

#### 22 258 ***Preparation before implementation***

23  
24 259 Before the commencement of the clinical trial, the investigators will be trained  
25  
26 260 on the trial protocol by the head of each trial center. Each investigator should  
27  
28 261 understand the content of this clinical trial protocol and master the standard methods  
29  
30 262 of enrollment, recording, and judgment criteria according to Standard Operating  
31  
32 263 Procedure (SOP) and Good Clinical Practice (GCP) guidelines. All participating  
33  
34 264 surgeons and residents should accept standard training on the unified assessment  
35  
36 265 methods for classifying different types of AA.

#### 37 266 ***Outcome measures***

##### 38 267 ***Primary outcome measure***

39  
40 268 The primary endpoint of this study is evaluation of the efficiency and long-term  
41  
42 269 outcome of ceftazidime combined with ornidazole compared with ceftazidime  
43  
44 270 combined with placebo. It is hypothesized that ceftazidime combined with ornidazole  
45  
46 271 is superior to ceftazidime combined with placebo and will increase the one-year cure  
47  
48 272 rate. The efficiency of nonoperative management (NOM) of uncomplicated  
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3 273 appendicitis will be measured on many aspects, including the initial cure rate, need  
4  
5 274 for operation, and long-term recurrence rate.  
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7

8 275 The definition of recurrence is based on clinical, imaging, and/or  
9  
10 276 histopathological diagnosis during follow-up. When subjects experience relevant  
11  
12 277 symptoms and signs, further laboratory inspection and imaging diagnosis of acute  
13  
14 278 appendicitis will be required. All patients with recurrent appendicitis will undergo a  
15  
16 279 laparoscopic appendectomy. Histopathological diagnosis results and bacterial culture  
17  
18 280 results during surgery will be recorded to identify recurrence.  
19  
20

### 21 281 *Secondary outcome measures*

22  
23  
24 282 Secondary endpoints are the evaluation of the total length of hospital stay, total  
25  
26 283 expenses during hospitalization, mortality, duration of antibiotic treatment,  
27  
28 284 complication rate, time to fulfill discharge criteria, pain score (VAS), the use of  
29  
30 285 analgesics, quality of life assessment (SF-12), readmission rate, percentage of patients  
31  
32 286 requiring appendectomy during initial antibiotic therapy, and the number of days  
33  
34 287 absent from work. Complications will be classified according to conservative  
35  
36 288 treatment, such as antibiotic-related adverse reactions, or surgery, such as the  
37  
38 289 incidence of surgical site infection (SSI), incisional hernia, anastomotic fistula,  
39  
40 290 abdominal abscess, and adhesions. The details of the data collection are shown in  
41  
42 291 Figure 2.  
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### 47 292 *Management and analysis of data*

#### 48 49 293 *Data collection and management*

50  
51 294 The data managers of the statistical unit are responsible for the data  
52  
53 295 management. At each subcenter, the complete raw information of patients will be  
54  
55 296 stored in electronic medical records and paper medical records to facilitate later  
56  
57 297 review. Baseline demographics, as well as the relevant variables of antibiotic  
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3 298 treatment and surgery, will be recorded independently by two data administrators. All  
4  
5 299 variables that need to be counted are provided in the full study protocol. These  
6  
7 300 variables should be registered in case report forms (CRFs), which will be entered into  
8  
9 301 ResMan, an electronic data collection and management system supported by the  
10  
11 302 Chinese Clinical Trial Registry. Data will be encrypted and can be processed only  
12  
13 303 with the authorization of the data managers. A detailed response questionnaire (DRQ)  
14  
15 304 will be used by the data managers to record missing and incorrect data. Then, the  
16  
17 305 investigator will verify the raw materials kept by the hospital.

### 306 *Statistical analysis*

307 The analysis of primary measures will be based on the intention-to-treat (ITT)  
308 set, and secondary outcomes will be analyzed with the per-protocol (PP) set. The  
309 safety analysis will be performed on the safety set. When ITT is used for analysis,  
310 missing results will be filled by statistical models based on their data distribution type.  
311 The sets are defined as follows:

- 312 1. ITT set: This set consists of all randomized subjects who have used the study  
313 drug at least once and have at least one postdrug efficacy evaluation.
- 314 2. PP set: This set includes all randomized subjects who complete all follow-ups  
315 as required by the protocol, have no major protocol violations, and have good  
316 compliance (medication compliance between 80%-120%).
- 317 3. Safety set: This set refers to all the subjects who entered the study, used the  
318 study drug at least once, and were evaluated for safety after using the medication.

319 All statistical analyses will be performed with SAS 9.1 system programming. All  
320 statistical tests, except for the superiority test (a one-sided test) of the primary  
321 measures, will be conducted on a bilateral basis. Continuous variables are described  
322 as the mean and standard deviation or median and upper and lower quartiles.

1  
2  
3 323 Categorical variables are described as the frequency and proportion. The one-sided  
4  
5 324 97.5% CI for proportion difference will be calculated to evaluate the treatment  
6  
7  
8 325 difference (one-sided test at  $\alpha=0.025$ ). The secondary outcomes will be analyzed  
9  
10 326 using different statistical methods according to the types of data. The t test or  
11  
12 327 Wilcoxon rank sum test is usually used to compare continuous variables between two  
13  
14 328 groups, and the chi-square test or Fisher's exact probability test is usually used to  
15  
16 329 compare categorical variables. P values less than 0.05 will be considered indicative of  
17  
18 330 statistical significance for all secondary outcome analyses.

### 331 ***Safety and data monitoring***

332 The statisticians in charge of randomization are responsible for the unblinding of  
333 information when subjects need to know the specific drugs used in case of emergency.  
334 In the case of adverse events, the observing physician can decide whether to terminate  
335 the observation based on the condition of the disease.

336 Regular on-site monitoring visits to the trial hospital will be conducted by  
337 designated personnel to ensure that all aspects of the clinical trial protocol are strictly  
338 followed and that the source data will be verified to ensure conformance with the  
339 CRFs. At the same time, the principal investigators and the heads of statistical  
340 analysis units will form a data management review committee (DMRC). Before the  
341 end of the follow-up and data locking, meetings must be held to individually review  
342 questionable data and/or the relationship between adverse events and drugs.

### 343 ***Ethics and dissemination***

#### 344 ***Ethics***

345 The protocol has acquired the approval of the Ethics Committee of Jinling  
346 Hospital on November 13, 2018(2018NZKY-027-01). This trial will be conducted

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3 347 following the Helsinki Declaration and the relevant Chinese clinical trial research  
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5 348 norms and regulations.  
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8 349 ***Patient and Public Involvement***  
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10 350 Patients or the public were not involved in the design, or conduct, or reporting,  
11  
12 351 or dissemination plans of our research  
13

14  
15 352 ***Protection of the rights and interests of patients***  
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17 353 Before the start of this trial, research physicians should inform patients of the  
18  
19 354 trial details in writing, including the nature of the clinical trial, the purpose of the trial,  
20  
21 355 the expected benefits and the risks. The researchers are responsible for protecting the  
22  
23 356 privacy of the participating patients. Even if the patients decide to withdraw from the  
24  
25 357 trial at any stage, their medical benefits and rights will not be affected in any way, and  
26  
27 358 they can continue to receive other effective treatment. For possible adverse events, the  
28  
29 359 experiment will also design corresponding solutions. In addition, after the experiment  
30  
31 360 is completed, the patients will be given the results by telephone. Translated written  
32  
33 361 consent is attached as a supplement file (Supplement Materials).  
34  
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36

37  
38 362 ***Dissemination plan***  
39

40 363 The trial findings will be published in peer-reviewed journals and will also be  
41  
42 364 disseminated through presentations at national and/or international conferences.  
43

44  
45 365 ***Discussion***  
46

47 366 The optimization of nonoperative management of appendicitis, including the  
48  
49 367 dosage form and duration of antibiotic use, is being actively researched.[15] However,  
50  
51 368 the types of antibiotics used in studies vary, and the selected antibiotics are not  
52  
53 369 common in many regions worldwide, such as low- and middle-level developing  
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55 370 countries. In addition, the role of anti-anaerobic agents in the treatment of  
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57 371 uncomplicated appendicitis remains to be explored and emphasized. These factors  
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3 372 make it difficult for clinicians to choose a reasonable antibiotic regimen for the  
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5 373 treatment of appendicitis.  
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8 374 According to our previous retrospective study, cephalosporin alone and  
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10 375 cephalosporin combined with nitroimidazole are common clinical treatment protocols  
11  
12 376 in China and have similar short-term outcomes in the treatment of uncomplicated AA.  
13  
14 377 However, few studies have compared the long-term outcomes of the different  
15  
16 378 treatment strategies due to the lack of follow-up information after discharge.[20] To  
17  
18 379 our knowledge, to date, no double-blinded randomized controlled trials have  
19  
20 380 compared three generations of cephalosporins combined with three generations of  
21  
22 381 cephalosporins combined with ornidazole in the treatment of uncomplicated AA.  
23  
24 382 Thus, we designed the OPTIMA trial to evaluate the safety and efficacy of a  
25  
26 383 combination of anti-anaerobic agents in the treatment of uncomplicated AA and its  
27  
28 384 prognostic impact. The results of this study are of great significance for guiding  
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30 385 clinical antibiotic use in an environment where antibiotic treatment regimens are not  
31  
32 386 standardized and rational.  
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### 37 ***Strengths and limitations of this study***

38  
39 388 In this trial, ultrasound, CT and MRI are both chosen as examination techniques  
40  
41 389 for appendicitis, since the accurate distinction between complicated and  
42  
43 390 uncomplicated AA is the key to rational treatment of appendicitis. Considering that  
44  
45 391 CT is not available at night at several nonteaching hospitals, patients with milder  
46  
47 392 conditions may be reluctant to undergo more expensive CT and MRI scans. If we  
48  
49 393 exclude these patients, it might increase the selection bias of the trial due to economic  
50  
51 394 and time factors. The overall sensitivity and specificity are 76% and 95% for  
52  
53 395 ultrasound and 99% and 84% for CT, respectively, and MRI is at least as sensitive  
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55 396 and specific as CT.[31-33] Moreover, recent studies have shown that the AIR score  
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3 397 has an advantage in diagnosing appendicitis due to its high sensitivity and  
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5 398 specificity.[25-30] Therefore, a combination of the AIR score and imaging will be  
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8 399 used to diagnose uncomplicated appendicitis in this study. All examination items and  
9  
10 400 results will be stored in a timely manner in the ResMan system, the data will be  
11  
12 401 verified and re-evaluated at any time by the dedicated data management review  
13  
14 402 committee (DMRC), and patients who do not meet the criteria for uncomplicated  
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16 403 appendicitis will be excluded. Thus, the diagnosis of noncomplicated AA in this trial  
17  
18  
19 404 is ensured to be reliable.

20  
21 405 In terms of antibiotic selection, ertapenem is a broad-spectrum antibiotic with an  
22  
23 406 anti-anaerobic effect that has been shown to be effective in the treatment of  
24  
25 407 appendicitis in previous studies and is recommended in the guidelines.[13] However,  
26  
27 408 compared with ertapenem, which is expensive and difficult to obtain, the antibiotics  
28  
29 409 chosen in this study are readily available and safe, which makes the optimized  
30  
31 410 nonoperative treatment of appendicitis obtained from the experimental results easier  
32  
33 411 to popularize. In addition, according to previous studies, antibiotic treatment for  
34  
35 412 uncomplicated acute appendicitis was shown to have the highest recurrence rate  
36  
37 413 during the first three months after discharge.[6, 7, 9] We speculate that this finding is  
38  
39 414 related to anaerobic bacteria in the intestinal tract. Thus, we plan to test this by  
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41 415 comparing ceftazidime plus placebo with ceftazidime plus ornidazole for  
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43 416 uncomplicated AA because of the excellent anti-anaerobic activity of nitroimidazoles.

44  
45 417 To date, this study has the largest sample size among uncomplicated AA studies  
46  
47 418 to evaluate the short-term and long-term prognoses. This study not only discusses the  
48  
49 419 efficacy of combined anti-anaerobic drugs in the treatment of uncomplicated  
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51 420 appendicitis but also focuses on the cure rate and recurrence rate of patients during the  
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3 421 follow-up period after discharge and explores methods for reducing the recurrence  
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5 422 rate of appendicitis.  
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8 423 For uncomplicated AA, it is difficult to obtain bacteriological evidence from the  
9  
10 424 patient's abdominal cavity. Therefore, the anti-anaerobic drugs were selected based on  
11  
12 425 a 2016 study of clinical characteristics and antimicrobial patterns in complicated  
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14 426 intra-abdominal infections in China.[34] In addition, a 2017 retrospective study of  
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16 427 appendicitis treatment reached similar conclusions about antibiotic use.[20]  
17  
18 428 Moreover, a sufficiently large sample and one year of standardized follow-up are  
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20 429 required to investigate the effect of anti-anaerobic drugs on the long-term outcome of  
21  
22 430 appendicitis. This is a challenge for the subcenters in how to conduct research  
23  
24 431 operations in an emergency department setting and how to respond promptly and  
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26 432 accurately to emergency problems.  
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### 30 433 **Conclusion**

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33 434 The OPTIMA trial is a multicenter, double-blinded, placebo-controlled,  
34  
35 435 superiority randomized study aiming to evaluate the role of anti-anaerobic bacterial  
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37 436 antibiotics in the resolution of uncomplicated AA.  
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### 42 438 **Declarations**

43  
44  
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46  
47 440 for providing the study drugs.  
48

49 441 **Authors' contributions:** All authors were involved in the study design, and read and  
50  
51 442 approved the final manuscript. J R, R S and P W contributed to conception and design  
52  
53 443 of this study. J W and H J provided statistical advice. J W, H J, S L and X W are  
54  
55 444 responsible for contacting with the subcenters. J R, R S, P W, X W and J W are  
56  
57 445 members of data management review committee. J W and H J drafted the manuscript.  
58  
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4 446 **Competing interests:** Jingdong Junzhuo Pharmaceutical Co., LTD provides the  
5  
6 447 study drugs (ornidazole and sodium chloride injection, ceftazidime injection and  
7  
8 448 simulants) for this investigator-initiated study but has no influence on the study  
9  
10 449 design, data analysis, or report. The investigators take full responsibility for the  
11  
12 450 integrity and content of this paper. And the authors declare that they have no  
13  
14  
15 451 competing interests.

16  
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18  
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20  
21  
22 454 and TGKS2019002).

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1  
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3 549 ***Figure legends***  
4

5 550 Figure 1: OPTIMA flowchart of enrollment, interventions, and follow-up.  
6

7 551 Abbreviation: ivgtt, intravenous drip; CRP, C reactive protein; VAS, Visual Analog  
8  
9 552 Scale.  
10

11 553 Figure 2: Follow-up schedule of OPTIMA. Abbreviation: VAS, Visual Analog Scale.  
12

13 554 \* Follow-up after discharge can be conducted either by telephone or in an outpatient  
14  
15 555 clinic as recommended.  
16

17 556 \*\* If symptoms of suspected appendicitis appear during follow-up after discharge,  
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19 557 relevant examinations should be performed and records should be made.  
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22 558 \*\*\* Patients undergoing surgical treatment should be recorded separately including  
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24 559 disease complications and surgical complications as well as their respective adverse  
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26 560 events.  
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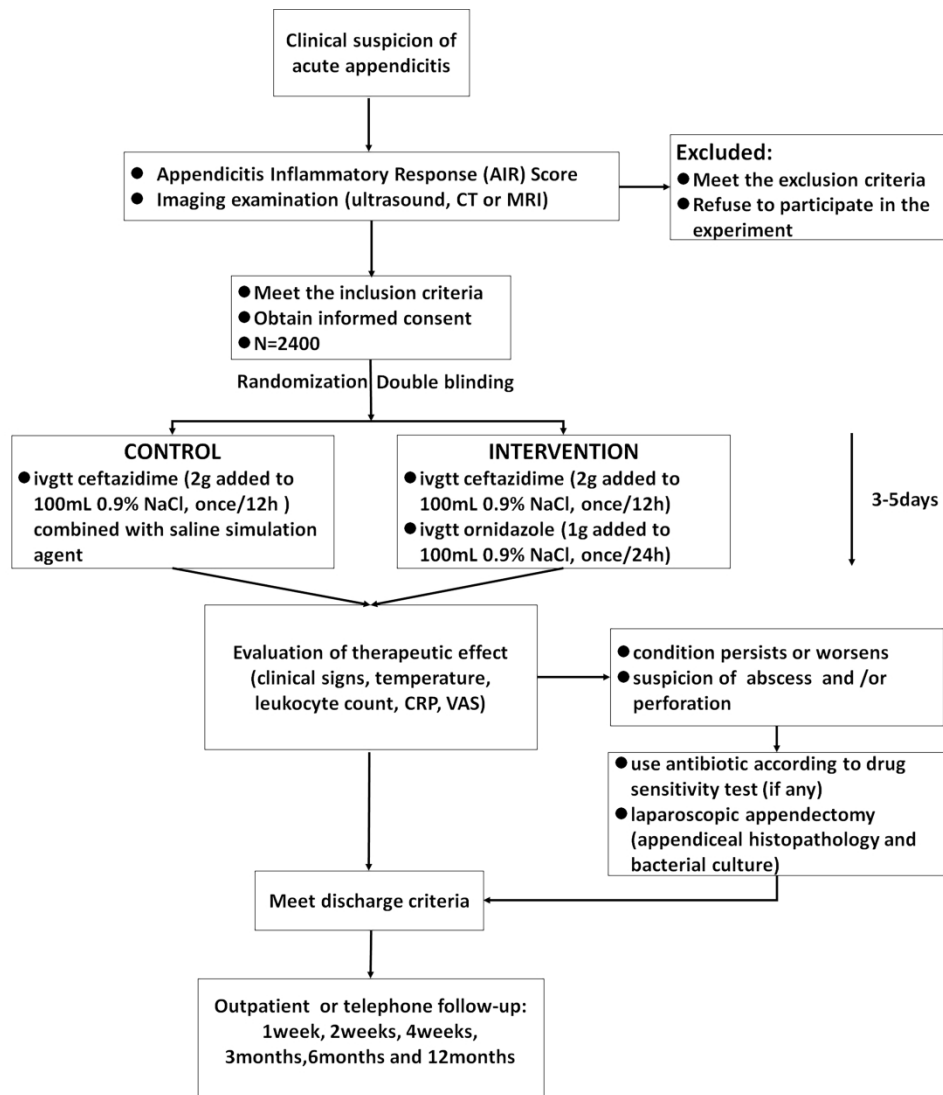


Figure 1: OPTIMA flowchart of enrollment, interventions, and follow-up. Abbreviation: ivgtt, intravenous drip; CRP, C reactive protein; VAS, Visual Analog Scale.

312x340mm (300 x 300 DPI)



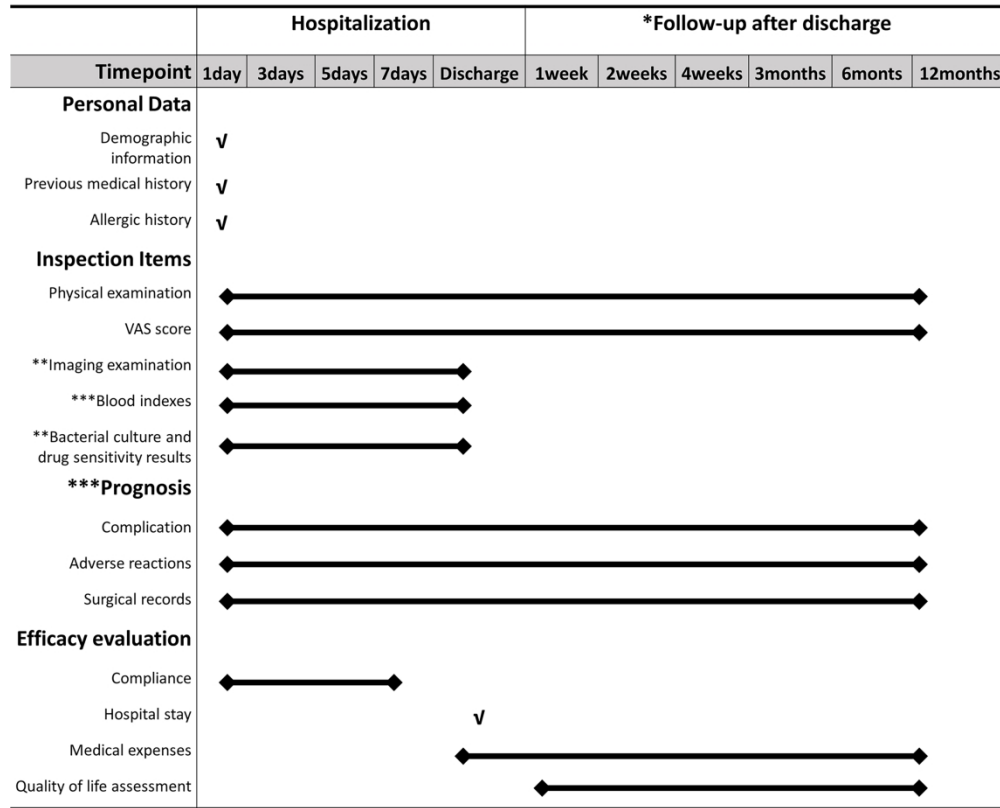


Figure 2: Follow-up schedule of OPTIMA. Abbreviation: VAS, Visual Analog Scale.

\* Follow-up after discharge can be conducted either by telephone or in an outpatient clinic as recommended.

\*\* If symptoms of suspected appendicitis appear during follow-up after discharge, relevant examinations should be performed and records should be made.

\*\*\* Patients undergoing surgical treatment should be recorded separately including disease complications and surgical complications as well as their respective adverse events.

328x265mm (300 x 300 DPI)

# CONSENT FORM

## PART I NOTICE TO PATIENTS

Dear patients and families,

We are going to carry out a “Optimizing the treatment for uncomplicated acute appendicitis: a multicentre, randomized double-blinded placebo-controlled study (OPTIMA trial)”. And you may meet the inclusion requirements of this study, therefore, we would like to invite you to participate in this study. We will introduce the purpose, process, benefits and risks of this study to you. Please read it carefully before deciding whether to participate in this study. You are able to ask questions and communicate when your doctor explains and discusses this informed consent. You can make your decision after full discussion with your family, friends and doctor.

If you are currently participating in another clinical study, please inform your doctor.

### WHY IS THIS STUDY BEING DONE?

Acute appendicitis (AA) is one of the most common indications for emergency surgery in the world. In 2019, there were an estimated 17.7 million cases (incidence 228/100,000). Appendectomy was first proposed by Mc Burney in 1894. For more than a century since then, appendectomy has been the golden standard treatment for appendicitis and has been widely applied in clinical practice. Although appendectomy is generally well tolerated, it is a major surgical intervention and can lead to some postoperative complications, such as bleeding, incision infection, adhesion of intestinal obstruction, fecal fistula, appendiceal stump inflammation. Therefore, how to treat acute appendicitis more effectively and safely has aroused the attention of clinicians.

Currently, laparoscopic surgery is widely used in the treatment of acute appendicitis. However, in recent years, more and more international clinical trials have confirmed that non-surgical treatment (conservative treatment) or conservative treatment followed by surgery have better therapeutic effects and lower incidence of complications. Conservative treatment also costs less, but there is a risk of recurrence. According to literature reports, the recurrence rate in Europe and America is 25%-35%. However, the choice of conservative treatment for appendicitis is varied and lack of medication standards. In addition, recent high-quality studies have reported that placebo treatment is as effective as antibiotic treatment for uncomplicated appendicitis in an Asian population.

Therefore, it is urgent for domestic clinicians to promote the standardized treatment of this most common disease in general surgery combined with national conditions and disease characteristics, so as to ensure the maximum efficacy and reduce the consumption of human, material and financial resources of patients.

## WHAT ARE THE OBJECTIVES OF THE STUDY?

To explore the difference in efficacy, complication rate and medical cost between ceftazidime combined with placebo and ceftazidime combined with ornidazole in the treatment of acute uncomplicated appendicitis.

## WHAT KIND OF PARTICIPANTS ARE NEEDED FOR THE STUDY?

2,400 acute appendicitis patients will be enrolled nationwide in accordance with government regulations and relevant institutional policies and procedures. The enrolled patients are eligible for the diagnosis of acute appendicitis, aged between 18 and 65 years old, and have no allergic reaction to the treatment drugs involved, no history of acute or chronic appendicitis, no liver or kidney dysfunction, sepsis and other symptoms. Female patients who are pregnant, in lactation or planning pregnancy will be excluded.

## STUDY PROCEDURE AND FOLLOW-UP SCHEDULE?

The study will be conducted by 80 centers nationwide, with 2,400 cases planned to be collected, led by the General Hospital of Eastern Theater Command. During the period of your participation in this clinical study, your doctor will collect your health information periodically to evaluate the effect of this treatment from the date of formal enrollment to 1 year after the end of your treatment.

We will assign you to ceftazidime combined with ornidazole or ceftazidime combined with placebo for no more than 7 days after you agree to enroll. The doctor will evaluate treatment effect at any time, take the effectiveness and safety of treatment as the first consideration, and perform surgical treatment for you if the conservative treatment effect is not ideal.

During the study period, you should not take any medications other than those prescribed or permitted by your study physician. For your safety and to ensure the effectiveness of the study, you should not participate in any other clinical studies involving drugs and medical devices during this period. Use effective contraceptive methods throughout the study period up to 2 weeks after treatment.

We will follow you up 1 day before treatment and 1 day, 3 days, 5 days, 7 days, 1 week, 2 weeks, 1 month, 3 months, half a year and 1 year after treatment according to your treatment status. The follow-up will cover your daily health status, discomfort and treatment-related complications. All measures based on your situation are required

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3 instead of additional examinations. If there is no need for further hospitalization, the  
4 follow-up after your treatment can be conducted by phone, outpatient service or  
5 WeChat, etc. Please confirm that you can cooperate with the doctor for follow-up within  
6 the specified follow-up time.  
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## 10 **ARE THERE BENEFITS TO TAKING PART IN THE STUDY?**

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Regardless of which group you are in, all ceftazidime and ornidazole used for your participation in this study will be provided free of charge, including ceftazidime and ornidazole used if conservative treatment fails and surgical treatment is required. However, the expenses related to other diseases shall be borne by you. Your doctor will closely observe you after your treatment and follow you up for at least 1 year, which will help to detect and treat any health problems during your follow-up. In the research process, professional doctors will do disease diagnosis, disease tracking observation, treatment guidance and disease consultation for you. The tests required to confirm your diagnosis, determine the extent of your disease, and assess the effect of your treatment are normal medical examinations, and this study will not add to your burden in this regard.

All drugs involved in this study have been approved in China for the treatment of patients with conditions similar to or even worse than yours. The information obtained from this study will help us develop a more reasonable, comprehensive and reliable diagnosis and treatment path and treatment norms for this disease, and promote it in patients with similar conditions to yours.

If the adverse reactions occurred during the study period due to the use of the study drugs need to be treated, the relevant expenses shall be covered by the company that provides drugs. If the adverse reactions are caused by medical negligence, the relevant expenses shall be borne by the relevant hospitals.

## WHAT ARE THE RISKS OF THE STUDY?

### **Recurrence**

Antimicrobial drugs can save you from surgical injury, but there is a certain risk of recurrence. According to the team's preliminary research results, the recurrence rate is 19% in Chinese population and 25%-35% in European and American population. But studies have shown that surgery after recurrence does not have a higher complication rate than surgery directly.

## Transferring to surgery

Conservative treatment of acute appendicitis may still require surgical treatment. However, according to existing reports, reoperation after the failure of conservative treatment does not increase the incidence of surgical complications.

## Adverse drug reaction

All drugs involved in this study have been extensively validated for safety and efficacy and have been approved for marketing by CFDA in China. But no drug is completely safe. During the treatment, you may not have any adverse reactions, or some drug-related adverse reactions may occur, but the adverse reactions mentioned in the study can be basically recovered after withdrawal.

According to the description in the drug instructions, the adverse reactions of the various drugs to be used in this study are as follows:

Ornidazole is generally well tolerated and the following reactions may occur during administration: 1. Digestive system: including mild stomach discomfort, nausea, bad breath, etc. 2. Nervous system: including dizziness and drowsiness, vertigo, etc.; 3. Irritation: rash, itchy, etc. 4. Others: leukopenia and so on

The adverse reactions of ceftazidime are rare and mild. A few patients may have skin rash, itching, drug fever; Nausea, diarrhea, abdominal pain; Mild phlebitis at the injection site; Occasionally transient elevation of serum aminotransferase, blood urea nitrogen and blood creatinine can occur. Leukopenia, thrombocytopenia and eosinophilia.

Your doctor and nurse will monitor your reaction at all times. If you experience any discomfort during the trial, you should inform your doctor at any time. Your doctor will give you other medications to relieve the discomfort. If you or your doctor determines that you cannot tolerate it, the study drug will be completely discontinued and you may be withdrawn from the study.

In addition to the risks of drugs, there are some related risks such as:

## Imaging examination

You will be exposed to a minuscule amount of radiation during the CT examination, but these are necessary for routine diagnosis and evaluation.

## Draw blood for examinations

The risks of taking blood from your arm include temporary discomfort and/or bruising. Infection, excessive bleeding, clotting, or fainting may occur, but they are highly unlikely.

## Operation

Any operation may have surgical complications, and appendectomy in this project may cause bleeding, incision infection, adhesive intestinal obstruction, fecal fistula, appendicitis, etc.

## WHAT ARE YOUR RIGHTS AS A PARTICIPANT?

You can choose not to participate in this study, which will have no adverse impact on your access to conventional treatment.

After you agree to participate in the study, you can change your mind at any time and tell the investigator to withdraw from the study in time. Your withdrawal will not affect your access to regular medical services. After the study is completed or discontinued, you will no longer be provided with the drugs in the study program free of charge.

## COMPENSATION?

Please inform your responsible investigator of any study related injury to your health during your participation in this study and provide your contact number \_\_\_\_\_. We will take the necessary medical measures. According to China's relevant laws and regulations, in case of irreversible injury related to the study, the person in charge of this study will deal with and treat it in time and provide corresponding economic compensation.

If you have questions related to the rights and interests of patients, you may contact the clinical trial ethics committee of your hospital at: \_\_\_\_\_.

## WHAT ABOUT CONFIDENTIALITY?

Your participation and personal data in the study are confidential. All study members and sponsors are required to keep your identity confidential. No personal information about you will be disclosed when the results of this study are published.

## PART II STATEMENT OF CONSENT AND AUTHORIZATION

### Patient informed consent Statement:

I have been informed of the research background, purpose, procedure, risks, benefits and rights of “Optimizing the treatment for uncomplicated acute appendicitis: a multicentre, randomized double-blinded placebo-controlled study (OPTIMA trial)”. I have ample time and opportunity to ask questions and I am satisfied with the answers. I am also told who to contact when I have questions or want further information. I have read this informed consent and agree to participate in this study. I know that during the study I can withdraw from the study at any point without any reason. I am told that I will get a copy of the informed consent, which contains my signature and that of the researcher.

Patient Signature:

Date:

Signature of Legal Representative [if applicable]:

Date:

Relationship with Patient:

When the patient or his/her legal representative is unable to read or write, at least one impartial witness must be present to confirm that the information in the informed consent has been correctly interpreted and that the patient and/or the subject's legal representative have understood the information. The patient voluntarily agreed to participate in the study.

Fair Witness Signature:

Date:

### Statement from the researchers

I have informed the patient (and his/her legal representative) of the background, objectives, procedures, risks, and benefits of the “Optimizing the treatment for uncomplicated acute appendicitis: a multicentre, randomized double-blinded placebo-controlled study (OPTIMA trial)”, and have given him/her sufficient time to read the informed consent, discuss with others, and answer his/her questions about the study; I have informed the patient of the contact information in case of problems; I have advised the patient (or legal representative) that he/she may withdraw from the study at any time during the study period without any reason.

Signature of Researchers:

Date:



STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description	Addressed on page number
<b>Administrative information</b>			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	P1/L1-3
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	P3/L53
	2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	3	Date and version identifier	
Funding	4	Sources and types of financial, material, and other support	P19/L448-450
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	P1/L4-L22
	5b	Name and contact information for the trial sponsor	P1/L13-20
	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	P18/L443
	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)	P14/L341



## 1 Introduction

2				
3	Background and	6a	Description of research question and justification for undertaking the trial, including summary of relevant	P4/L70-133
4	rationale		studies (published and unpublished) examining benefits and harms for each intervention	
5				
6		6b	Explanation for choice of comparators	P5/L101-113
7				
8	Objectives	7	Specific objectives or hypotheses	P5/L114-118
9				
10	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group),	
11			allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	P5/L121-128
12				
13				
14	<b>Methods: Participants, interventions, and outcomes</b>			
15				
16	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will	P6/L130
17			be collected. Reference to where list of study sites can be obtained	
18				
19	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and	P6/L148-170
20			individuals who will perform the interventions (eg, surgeons, psychotherapists)	P11/L260-266
21				
22	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be	P10/L224-234
23			administered	
24		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose	P10/L236-242
25			change in response to harms, participant request, or improving/worsening disease)	
26		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence	P11/L252-256
27			(eg, drug tablet return, laboratory tests)	
28		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	P10/L236-242
29				
30	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood	P11/L268-292
31			pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg,	
32			median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen	
33			efficacy and harm outcomes is strongly recommended	
34	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for	P6/L121-128
35			participants. A schematic diagram is highly recommended (see Figure)	
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1	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	P8/L197-217
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4	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	P10/L219-221
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7	<b>Methods: Assignment of interventions (for controlled trials)</b>			
8	Allocation:			
9				
10	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	P7/L172-186
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16	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	P8/L188-195
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20	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	P8/L183
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24	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	P8/L183,188-195
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27		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	P14/L333-336
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31	<b>Methods: Data collection, management, and analysis</b>			
32				
33	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	P13/L320-331
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39		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	P11/L250-256
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1	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	P12/L295-306
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5	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	P13/308-331
6				
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8		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	P13/L308-319
9				
10		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	P13/L310-312
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14	<b>Methods: Monitoring</b>			
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16	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	P14/L340-341
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22		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	P14/L341-343
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25	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	P12/L287-290
26				
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28	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	P14/L341-343
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32	<b>Ethics and dissemination</b>			
33				
34	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	P14/L346-349
35				
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37	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)	Not applicable
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1	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	P15/L354-361
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4		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Detail in informed consent form
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8	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	Detail in informed consent form
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13	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	P18/L443-447
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16	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	P19/L451-456
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19	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	Detail in informed consent form
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24	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, health care professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	P15/L362-364
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28		31b	Authorship eligibility guidelines and any intended use of professional writers	Not applicable
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30		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Not applicable
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33	<b>Appendices</b>			
34	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	See supplement materials
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39	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	Not applicable
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1 \*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.  
2 Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons  
3 "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.  
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# BMJ Open

## Optimizing the treatment for uncomplicated acute appendicitis (OPTIMA trial): A protocol for a multicenter, randomized double-blinded placebo-controlled study

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Complete List of Authors:	Wu, Jie; The Affiliated BenQ Hospital of Nanjing Medical University, Department of General surgery Jiang, Haiyang; The Affiliated BenQ Hospital of Nanjing Medical University, Department of General surgery Li, Shikuan; The Affiliated Hospital of Qingdao University, Department of Emergency Medicine Wu, Xiuwen; Nanjing Jinling Hospital, Department of Surgery, Jinling Hospital, Nanjing Medical University, Nanjing, Jiangsu Province, China. Wang, Peige; The Affiliated Hospital of Qingdao University, Department of Emergency Medicine Sawyer, Robert; Western Michigan University, General Surgery Department Ren, Jianan; Nanjing Jinling Hospital, Department of Surgery, Jinling Hospital, Nanjing Medical University, Nanjing, Jiangsu Province, China.
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Secondary Subject Heading:	Emergency medicine
Keywords:	ACCIDENT & EMERGENCY MEDICINE, Adult gastroenterology < GASTROENTEROLOGY, Gastrointestinal infections < GASTROENTEROLOGY

SCHOLARONE™  
Manuscripts

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3 1 Optimizing the treatment for uncomplicated acute appendicitis (OPTIMA  
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6 2 trial): A protocol for a multicenter, randomized double-blinded placebo-  
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9 3 controlled study

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11 4 Jie Wu<sup>1a</sup>, Haiyang Jiang<sup>1,a</sup>, Shikuan Li<sup>2</sup>, Xiuwen Wu<sup>3</sup>, Peige Wang<sup>2\*</sup>, Robert  
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13  
14 5 Sawyer<sup>4\*</sup>, Jianan Ren<sup>3\*</sup>

15  
16 6 1 Department of Surgery, BenQ Medical Centre, The Affiliated BenQ Hospital of Nanjing  
17  
18 7 Medical University, Nanjing, Jiangsu Province, China.

19  
20 8 2 Department of Emergency Medicine, The Affiliated Hospital of Qingdao University

21  
22 9 3 Department of Surgery, Jinling Hospital, Nanjing Medical University, Nanjing, Jiangsu  
23  
24 10 Province, China.

25  
26 11 4 General Surgery Department, Western Michigan University, Kalamazoo, MI, USA.

27  
28  
29 12

30  
31 13 \* Correspondence to:

32  
33 14 Peige Wang, 16 Jiangsu Road, Qingdao, 266000, People's Republic of China. E-mail:  
34  
35 15 wpgzyz@163.com.

36  
37 16 Robert Sawyer, Western Michigan University Homer Stryker MD School of Medicine  
38  
39 17 1000 Oakland Drive, Kalamazoo, MI 49008 USA. E-mail:

40  
41 18 [Robert.Sawyer@med.wmich.edu](mailto:Robert.Sawyer@med.wmich.edu)

42  
43 19 Jianan Ren, Department of Surgery, Jinling Hospital, 305 East Zhongshan Road, Nanjing,  
44  
45 20 210002, China. E-mail: [jiananr@gmail.com](mailto:jiananr@gmail.com)

46  
47 21 Telephone: +8613605169808

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49 22 a These authors contributed equally to this work

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51 23 Word count:3984

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3 **Abstract**  
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5 **Introduction** Emerging evidence has shown that an antibiotics-first strategy is a  
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viable treatment option for uncomplicated acute appendicitis (AA). Although there  
has recently been an interest and increase in the use of antibiotics as the primary  
strategy for treating uncomplicated AA, there is no consensus regarding the optimum  
antibiotic regimen. In particular, the long-term outcomes of different antibiotic  
regimens, such as the recurrence rate, still lack evidence. Given that the flora of the  
appendix is mainly anaerobic bacteria and that a Korean open-label study showed a  
higher proportion of recurrence in the symptomatic treatment group than antibiotic  
group, we hypothesized that anti-anaerobe regimens could decrease the recurrence  
rate compared to those that did not include anti-anaerobic antibiotics.

**Methods and analysis:** The OPTIMA trial is a multicenter, double-blind, placebo-  
controlled, superiority randomized study aiming to evaluate the role of anti-anaerobic  
antibiotics in the resolution of uncomplicated AA. Patients (18-65years) with  
uncomplicated AA (without gangrenous and/or perforated appendicitis or appendiceal  
abscess or appendiceal fecaliths) are eligible for inclusion. The primary endpoint of  
this study is the success rate of the treatment, defined as the resolution of AA  
resulting in discharge from the hospital without surgical intervention and recurrent  
symptoms within 1 year. Secondary endpoints include mortality, postintervention  
complications, recurrent symptoms up to 1 year after treatment, hospital stay, sick  
leave, treatment cost, pain symptom scores, and quality of life. Data are reported as  
the number of cases (%), median (range), and relative risk and will be analyzed using  
the Mann–Whitney U test or chi-square test, as appropriate, and a P value < 0.05 will  
be considered significant.



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3 49 **Ethics and dissemination:** The protocol has acquired the approve of the Ethics  
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5 50 Committee of Jinling Hospital on November 13, 2018(2018NZKY-027-01). The trial  
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7 51 findings will be published in peer-reviewed journals.  
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10 52 **Trial registration:** Chinese Clinical Trial Register, ChiCTR1800018896  
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### 12 53 **Strengths and limitations of this study**

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14 54 Strength 1: The OPTIMA trial is the first multicenter, randomized, double-blinded,  
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16 55 placebo-controlled clinical study comparing ceftazidime combined with ornidazole  
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18 56 versus ceftazidime combined with placebo for uncomplicated acute appendicitis to  
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20 57 investigate the role of anti-anaerobic drugs in the conservative treatment of  
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22 58 appendicitis.  
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26 59 Strength 2: A double-blinded trial with a placebo can reduce bias and confirm the role  
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28 60 of anti-anaerobic agents in the treatment of appendicitis.  
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31 61 Strength 3: The data will be collected and saved in an electronic data capture system  
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33 62 (EDC) to guarantee the integrity of the data, and the data engineers will organize and  
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35 63 check the data from each center to reduce errors in the data collection process.  
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38 64 Limitation 1: Since the treatment of uncomplicated appendicitis in this study involves  
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40 65 antibiotics alone, we cannot collect data on surgical pathology and bacteriological  
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42 66 analysis, unless surgical intervention is required.  
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45 67

### 46 68 **Introduction**

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48  
49 69 Acute appendicitis (AA) is one of the most common indications for emergency  
50  
51 70 surgery worldwide.[1] In 2019, there were an estimated 17.7 million cases (incidence,  
52  
53 71 228/100,000).[2] Appendectomy was first proposed by Mc Burney in 1894.[3] For  
54  
55 72 more than a century since then, appendectomy has been the gold standard treatment  
56  
57 73 for appendicitis and has been widely applied in clinical practice. However, the  
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2  
3 74 treatment of AA has been under active debate and discourse in recent years, and an  
4  
5 75 increasing amount of evidence has shown that the majority of patients with  
6  
7 76 uncomplicated acute appendicitis can be treated with antibiotics alone instead of  
8  
9  
10 77 surgery.[4-12] Therefore, the guidelines recommend antibiotic treatment for  
11  
12 78 uncomplicated AA when patients accept the recurrence risk.[13]

13  
14  
15 79 At present, there is no consensus on the choice of antibiotics, and various  
16  
17 80 antibiotic regimens have been adopted. Some recent clinical studies have focused on  
18  
19 81 defining a better regimen, including the route of administration, course of treatment  
20  
21 82 and even supportive care without antibiotics.[5, 14-19] A randomized clinical trial on  
22  
23 83 antibiotic therapy for uncomplicated AA from Finland adopted antibiotic therapy with  
24  
25 84 intravenous ertapenem for 3 days followed by 7 days of oral levofloxacin and  
26  
27 85 metronidazole and showed that antibiotic therapy is noninferior to appendectomy.  
28  
29 86 [15] Park et al. performed a single-blinded (participants only) trial and reported  
30  
31 87 results regarding possible spontaneous resolution of uncomplicated acute appendicitis.  
32  
33 88 [16] Recently, the APPAC group designed and published a protocol for a multicenter,  
34  
35 89 double-blinded, placebo-controlled, superiority randomized study comparing  
36  
37 90 antibiotic therapy with placebo for the treatment of CT scan-confirmed uncomplicated  
38  
39 91 acute appendicitis, aiming to evaluate the role of antibiotics in the resolution of  
40  
41 92 uncomplicated acute appendicitis (NCT03234296).

42  
43  
44 93 However, the antibiotics used in these trials are not the preferred choice in most  
45  
46 94 countries, including China. According to our previous study, three generations of  
47  
48 95 intravenously administered cephalosporins with or without nitroimidazoles are the  
49  
50 96 most common regimens, and the usage of antimicrobial drug regimens in conservative  
51  
52 97 treatment for AA lacks standardization and rationale.[20] Additionally, the usage of  
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3 98 antibiotic regimens in clinical trials or guidelines also varies, which can cause  
4  
5 99 confusion for physicians regarding the choice of conservative AA treatment.  
6  
7

8 100 The trial from Park et al. showed a higher tendency of recurrence of appendicitis  
9  
10 101 in the no-antibiotic group than in the antibiotic group. Considering Park's study was  
11  
12 102 not a double-blind and multicenter study, it is necessary to conduct more larger  
13  
14 103 sample size trials to prove the correctness of the conclusion.[16] In addition,  
15  
16 104 cephalosporins combined with nitroimidazoles as preoperative prophylactic antibiotic  
17  
18 105 regimens have been proven to reduce the incidence of surgical site infection compared  
19  
20 106 with cephalosporins alone in both noncomplicated and complicated AA patients.[21]  
21  
22 107 A prospective double-blinded randomized controlled trial revealed a significant  
23  
24 108 decrease in wound infection rates with 2 postoperative intravenous doses of  
25  
26 109 antibiotics, suggesting that postoperative antibiotics are of benefit in simple  
27  
28 110 appendicitis.[22] Some etiological studies also suggested that anaerobic bacteria in  
29  
30 111 uncomplicated appendicitis are a nonnegligible risk factor for disease progression.[23-  
31  
32 112 26] Accordingly, we hypothesized that a combination of anti-anaerobe drug regimens  
33  
34 113 would have stronger effects on decreasing the recurrence of AA.  
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40 114 To our knowledge, this double-blinded randomized controlled study is the first to  
41  
42 115 evaluate the therapeutic efficiency (a composite primary outcome including in-  
43  
44 116 hospital cure rate, transfer rate and recurrence rate within a one year follow-up period)  
45  
46 117 of the anti-anaerobe covered strategy compared to anti-anaerobic uncovered regimens  
47  
48 118 in uncomplicated AA, providing a reference for rational antibiotic selection.  
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## 51 119 *Methods*

### 52 120 *Trial design*

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56 121 The OPTIMA trial is a multicenter, randomized, double-blinded, parallel  
57  
58 122 controlled clinical trial designed to evaluate the therapeutic qualities and efficiency of  
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3 123 a combination anti-anaerobe strategy compared with no use of anti-anaerobic agents.  
4  
5 124 At each center, patients are randomly allocated to the experimental treatment arm  
6  
7 125 (intravenously administered ceftazidime combined with ornidazole) or the control arm  
8  
9 126 (intravenously administered ceftazidime combined with a saline simulation agent) in a  
10  
11 127 1:1 ratio. Figure 1 shows the enrollment process, interventions, and follow-up of  
12  
13 128 participants in two conservative treatments for acute appendicitis.  
14  
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16

### 17 129 ***Trial setting***

18  
19 130 The trial will take place at 80 hospitals in China. All participating hospitals will  
20  
21 131 recruit a specified number of patients according to the annual admission volume of  
22  
23 132 each center. At all participating hospitals, appendectomy is usually performed  
24  
25 133 laparoscopically.  
26  
27

### 28 134 ***Diagnosis***

29  
30 135 A rapid and correct diagnosis of uncomplicated appendicitis is the key to the  
31  
32 136 success of the study. First, imaging has irreplaceable advantages in the diagnosis and  
33  
34 137 differentiation of uncomplicated appendicitis. Moreover, due to the high sensitivity  
35  
36 138 and specificity of the appendicitis inflammatory response (AIR) score in the  
37  
38 139 identification of advanced appendicitis, we combined the AIR score and imaging tests  
39  
40 140 to diagnose uncomplicated appendicitis.[27-32] All patients with clinically suspected  
41  
42 141 AA will be enrolled for further screening. Clinical history, physical examination and  
43  
44 142 laboratory tests, including routine blood tests (white cell count, proportion of  
45  
46 143 polymorphonuclear leukocytes), C-reactive protein (CRP), creatinine, and female  
47  
48 144 human chorionic gonadotropin (HCG), will be evaluated by the surgeon. The AIR  
49  
50 145 score will be recorded according to the inspection results to define three groups: low  
51  
52 146 probability (<5 points), medium probability (5–8 points), and high probability (>8  
53  
54 147 points). Then, all patients will undergo imaging.  
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3 148 ***Inclusion criteria:***  
4

5 149 1. Age 18-65 years  
6

7 150 2. AIR score: low probability (<5 points), medium probability (5–8 points)  
8

9 151 3. Diagnosis of uncomplicated AA confirmed by imaging (ultrasound, CT or  
10

11 152 MRI) defined by the following criteria: appendix diameter greater than 6 mm,  
12

13 153 thickened appendix wall, appendix lumen stenosis, inflammatory edema and a small  
14

15 154 amount of effusion around the appendix.  
16

17  
18  
19 155 ***Exclusion criteria:***  
20

21 156 1. Age <18 or >65  
22

23 157 2. AIR score >8  
24

25 158 3. Diagnosis of existing complications by imaging (ultrasound, CT or MRI), such  
26

27 159 as abscess, appendiceal fecalith, or perforation  
28

29 160 4. Appendiceal tumor and/or appendiceal soft tissue mass  
30

31 161 5. History of acute or chronic appendicitis  
32

33 162 6. Suspicion of severe sepsis  
34

35 163 7. Patients with a known history of allergies or other contraindications to the  
36

37 164 study antibiotics  
38

39 165 8. Immunocompromised patients  
40

41 166 9. Patients undergoing other antibiotic treatments  
42

43 167 10. Alcoholics  
44

45 168 11. Women who are pregnant or plan to become pregnant or who are  
46

47 169 breastfeeding within 3 months of the study  
48

49 170 12. Refusal to sign the informed consent  
50

51 171 ***Allocation and randomisation***  
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1  
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3 172 Due to differences in the volume of visits from each hospital, the data analyst  
4  
5 173 will assign a fixed number of cases to each subcenter based on its annual volume of  
6  
7 174 visits. SAS 9.1 software will be used to achieve stratified block randomization. The  
8  
9 175 researchers will be blinded to the stratified randomization process and the results of  
10  
11 176 patient randomization. At each center, after signing the informed consent, the patients  
12  
13 177 meeting the trial criteria will be randomly assigned to arm A (ceftazidime combined  
14  
15 178 with placebo group) or arm B (ceftazidime combined with ornidazole group) in a 1:1  
16  
17 179 ratio. Each patient will be given a unique study number, undergo random grouping  
18  
19 180 and be assigned a designated treatment with ‘Jinling Rat’ random allocation software.  
20  
21 181 The pharmacists will obtain treatment packages in similar containers that are  
22  
23 182 distinguishable only by a patient's unique identification number. To ensure patient  
24  
25 183 safety in an emergency, data analysts will provide each hospital with an emergency  
26  
27 184 unblinding list that includes the specific drugs used by the patients participating in the  
28  
29 185 trial. Each hospital should use it only in critical situations, such as when a patient has  
30  
31 186 severe allergies to the treatment drug in the study.  
32  
33  
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### 37 **Blinding**

38  
39 188 Jinling Rat software is a random allocation tool used to maintain double  
40  
41 189 blinding throughout the whole process of the trial. The investigators and the patients  
42  
43 190 remain unaware of the treatment packages until the study is finished and the data have  
44  
45 191 been locked.  
46  
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48

49 192 Follow-up will be conducted by the surgeon at each center either by telephone  
50  
51 193 or outpatient visits. The surgeon who performs the follow-up is not aware of the  
52  
53 194 patient's previous antibiotic regimen and records only the required information on the  
54  
55 195 follow-up form.  
56  
57

### 58 **Sample size calculation**

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1  
2  
3 197 Given the results of previous studies indicating that antibiotics have a success  
4  
5 198 rate of approximately 75% in treating uncomplicated appendicitis, the recurrence rate  
6  
7  
8 199 within one year is 25-35%, and the recurrence rate with antibiotic treatment for  
9  
10 200 appendicitis is highest within the three months after discharge,[7, 9, 15, 16] we  
11  
12 201 estimate that the success rate of the combination of anti-anaerobic drugs can increase  
13  
14 202 the cure rate from 75% to 80%. Under this condition, we calculated that a minimum  
15  
16 203 of 1091 patients in each group would achieve a power of 0.8 ( $1-\beta$ ) and a one-sided  
17  
18 204 significance level ( $\alpha$ ) of 0.025 to conclude that the efficacy of the intervention arm is  
19  
20 205 superior to that of the control arm regarding the long-term cure rate.  
21  
22  
23

24 206 In addition, some relevant studies have chosen short-term efficacy as the primary  
25  
26 207 outcome considering that AA is an acute phase disease and that antibiotics will not  
27  
28 208 have effects on subjects after drug metabolism. Therefore, those studies have selected  
29  
30 209 the response rate after a course of drug therapy as the primary outcome. Under this  
31  
32 210 condition, we projected a sample size of 564 participants for each group with 90%  
33  
34 211 power at a two-sided alpha level of 0.05 using PASS software (PASS 11, NCSS  
35  
36 212 software, Kaysville, USA) to conclude that the efficacy of the intervention arm is  
37  
38 213 superior to that of the control arm (from 96% to 99%).  
39  
40  
41

42 214 Therefore, to sufficiently analyze both the short- and long-term efficacy of  
43  
44 215 antibiotic therapy, we chose the first algorithm for sample size estimation, and a total  
45  
46 216 of 2400 patients will be recruited, given an estimated dropout rate of 10% of all  
47  
48 217 patients.  
49

### 50 51 218 ***Recruitment plan***

52  
53 219 Recruitment of participants will start in January 2022 and follow-ups should be  
54  
55 220 carried out at the same time. All 2400 patients are expected to be enrolled by the end  
56  
57 221 of 2022.  
58  
59  
60

## 222 ***Interventions***

### 223 ***Antibiotic use protocol***

224 Patients will be randomly assigned in a 1:1 ratio to either the experimental  
225 treatment arm (intravenously administered ceftazidime combined with ornidazole) or  
226 the control arm (intravenously administered ceftazidime combined with an ornidazole  
227 simulation agent). The experimental treatment group will receive ceftazidime (2 g  
228 added to 100 mL 0.9% NaCl injection for intravenous drip, once every 12 h) +  
229 ornidazole (1 g added to 100 mL 0.9% NaCl injection for intravenous drip, once every  
230 24 h) for 3-5 d of routine treatment. The control group will receive ceftazidime (2 g  
231 added to 100 mL 0.9% NaCl injection for intravenous drip, once every 12 h) +  
232 simulation agent (two doses added to 100 mL 0.9% NaCl injection for intravenous  
233 drip, once every 12 h) for 3-5 d of routine treatment. In both groups, the maximum  
234 extension will not be more than 7 d, depending on the treatment response.

### 235 ***Criteria for transferring to another treatment***

236 In the case of a confirmed source of infection through the drug sensitivity test,  
237 appropriate antimicrobial agents can be adopted. If conservative treatment for 24 h is  
238 not effective or the patient's condition worsens, the treatment strategies should be  
239 switched immediately. When an exacerbation of the infection or the occurrence of  
240 perforated appendicitis or diffuse peritonitis is suspected, patients will undergo an  
241 emergency laparoscopic appendectomy and appendiceal histopathology and bacterial  
242 culture.

### 243 ***Discharge and follow-up***

244 Patients meeting the clinical cure criteria will be discharged, which means that  
245 the following criteria must be met at the same time: body temperature (underarm)  
246 <37.5°C, white blood cell count <10.0×10<sup>9</sup>/L, neutrophil percentage <70%, and no



1  
2  
3 247 deep tenderness, mass or rebound pain in the right lower abdomen of the subjects  
4  
5 248 during follow-up after treatment with the medication. According to the duration of  
6  
7 249 conservative treatment, the hospitalization follow-up time will be set to 1 week. The  
8  
9  
10 250 following indicators will be collected on days 1, 3, 5, and 7: a physical examination,  
11  
12 251 including the Visual Analog Scale (VAS), auxiliary examination, therapeutic effect,  
13  
14 252 and surgery status (if any). An outpatient follow-up visit is recommended one week  
15  
16 253 after discharge. Standard follow-ups of 2 weeks, 1 month, 3 months, 6 months, and 1  
17  
18 254 year will be performed by the surgeon either by telephone or in an outpatient setting.  
19  
20 255 For patients treated surgically, follow-up should include the assessment of surgical  
21  
22 256 site infection (SSI) in one month.

23  
24  
25  
26 257 If the patient is treated conservatively or surgically for recurrent appendicitis  
27  
28 258 after discharge, the time and components of treatment should be recorded.

### 29 30 259 ***Preparation before implementation***

31  
32  
33 260 Before the commencement of the clinical trial, the investigators will be trained  
34  
35 261 on the trial protocol by the head of each trial center. Each investigator should  
36  
37 262 understand the content of this clinical trial protocol and master the standard methods  
38  
39 263 of enrollment, recording, and judgment criteria according to Standard Operating  
40  
41 264 Procedure (SOP) and Good Clinical Practice (GCP) guidelines. All participating  
42  
43 265 surgeons and residents should accept standard training on the unified assessment  
44  
45 266 methods for classifying different types of AA.

### 46 47 48 49 267 ***Outcome measures***

#### 50 51 268 ***Primary outcome measure***

52  
53  
54 269 The primary endpoint of this study is evaluation of the efficiency and long-term  
55  
56 270 outcome of ceftazidime combined with ornidazole compared with ceftazidime  
57  
58 271 combined with placebo. It is hypothesized that ceftazidime combined with ornidazole  
59  
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1  
2  
3 272 is superior to ceftazidime combined with placebo and will increase the one-year cure  
4  
5 273 rate. The efficiency of nonoperative management (NOM) of uncomplicated  
6  
7 274 appendicitis will be measured on many aspects, including the initial cure rate, need  
8  
9 275 for operation, and long-term recurrence rate.

10  
11  
12 276 The definition of recurrence is based on clinical, imaging, and/or  
13  
14 277 histopathological diagnosis during follow-up. When subjects experience relevant  
15  
16 278 symptoms and signs, further laboratory inspection and imaging diagnosis of acute  
17  
18 279 appendicitis will be required. All patients with recurrent appendicitis will undergo a  
19  
20 280 laparoscopic appendectomy. Histopathological diagnosis results and bacterial culture  
21  
22 281 results during surgery will be recorded to identify recurrence.

## 26 282 ***Secondary outcome measures***

27  
28 283 Secondary endpoints are the evaluation of the total length of hospital stay, total  
29  
30 284 expenses during hospitalization, mortality, duration of antibiotic treatment,  
31  
32 285 complication rate, time to fulfill discharge criteria, pain score (VAS), the use of  
33  
34 286 analgesics, quality of life assessment (SF-12), readmission rate, percentage of patients  
35  
36 287 requiring appendectomy during initial antibiotic therapy, and the number of days  
37  
38 288 absent from work. Complications will be classified according to conservative  
39  
40 289 treatment, such as antibiotic-related adverse reactions, or surgery, such as the  
41  
42 290 incidence of surgical site infection (SSI), incisional hernia, anastomotic fistula,  
43  
44 291 abdominal abscess, and adhesions. The details of the data collection are shown in  
45  
46 292 Figure 2.

## 51 293 ***Management and analysis of data***

### 53 294 ***Data collection and management***

54  
55  
56 295 The data managers of the statistical unit are responsible for the data  
57  
58 296 management. At each subcenter, the complete raw information of patients will be  
59  
60

1  
2  
3 297 stored in electronic medical records and paper medical records to facilitate later  
4  
5 298 review. Baseline demographics, as well as the relevant variables of antibiotic  
6  
7 299 treatment and surgery, will be recorded independently by two data administrators. All  
8  
9  
10 300 variables that need to be counted are provided in the full study protocol. These  
11  
12 301 variables should be registered in case report forms (CRFs), which will be entered into  
13  
14 302 ResMan, an electronic data collection and management system supported by the  
15  
16 303 Chinese Clinical Trial Registry. Data will be encrypted and can be processed only  
17  
18 304 with the authorization of the data managers. A detailed response questionnaire (DRQ)  
19  
20 305 will be used by the data managers to record missing and incorrect data. Then, the  
21  
22 306 investigator will verify the raw materials kept by the hospital.  
23  
24  
25

### 26 307 ***Statistical analysis***

27  
28 308 The analysis of primary measures will be based on the intention-to-treat (ITT)  
29  
30 309 set, and secondary outcomes will be analyzed with the per-protocol (PP) set. The  
31  
32 310 safety analysis will be performed on the safety set. When ITT is used for analysis,  
33  
34 311 missing results will be filled by statistical models based on their data distribution type.  
35  
36 312 The sets are defined as follows:  
37  
38  
39

40 313 1. ITT set: This set consists of all randomized subjects who have used the study  
41  
42 314 drug at least once and have at least one postdrug efficacy evaluation.

43  
44 315 2. PP set: This set includes all randomized subjects who complete all follow-ups  
45  
46 316 as required by the protocol, have no major protocol violations, and have good  
47  
48 317 compliance (medication compliance between 80%-120%).

49  
50 318 3. Safety set: This set refers to all the subjects who entered the study, used the  
51  
52 319 study drug at least once, and were evaluated for safety after using the medication.  
53

54  
55 320 All statistical analyses will be performed with SAS 9.1 system programming. All  
56  
57 321 statistical tests, except for the superiority test (a one-sided test) of the primary  
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1  
2  
3 322 measures, will be conducted on a bilateral basis. Continuous variables are described  
4  
5 323 as the mean and standard deviation or median and upper and lower quartiles.  
6  
7 324 Categorical variables are described as the frequency and proportion. The one-sided  
8  
9 325 97.5% CI for proportion difference will be calculated to evaluate the treatment  
10  
11 326 difference (one-sided test at  $\alpha=0.025$ ). The secondary outcomes will be analyzed  
12  
13 327 using different statistical methods according to the types of data. The t test or  
14  
15 328 Wilcoxon rank sum test is usually used to compare continuous variables between two  
16  
17 329 groups, and the chi-square test or Fisher's exact probability test is usually used to  
18  
19 330 compare categorical variables. P values less than 0.05 will be considered indicative of  
20  
21 331 statistical significance for all secondary outcome analyses.  
22  
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25

### 26 332 ***Safety and data monitoring***

27  
28 333 The statisticians in charge of randomization are responsible for the unblinding of  
29  
30 334 information when subjects need to know the specific drugs used in case of emergency.  
31  
32 335 In the case of adverse events, the observing physician can decide whether to terminate  
33  
34 336 the observation based on the condition of the disease.  
35  
36  
37

38 337 Regular on-site monitoring visits to the trial hospital will be conducted by  
39  
40 338 designated personnel to ensure that all aspects of the clinical trial protocol are strictly  
41  
42 339 followed and that the source data will be verified to ensure conformance with the  
43  
44 340 CRFs. At the same time, the principal investigators and the heads of statistical  
45  
46 341 analysis units will form a data management review committee (DMRC). Before the  
47  
48 342 end of the follow-up and data locking, meetings must be held to individually review  
49  
50 343 questionable data and/or the relationship between adverse events and drugs.  
51  
52  
53

### 54 344 ***Ethics and dissemination***

#### 55 56 345 ***Ethics***

1  
2  
3 346 The protocol has acquired the approval of the Ethics Committee of Jinling  
4  
5 347 Hospital on November 13, 2018(2018NZKY-027-01). This trial will be conducted  
6  
7  
8 348 following the Helsinki Declaration and the relevant Chinese clinical trial research  
9  
10 349 norms and regulations.

### 11 12 350 *Patient and Public Involvement*

13  
14  
15 351 Patients or the public were not involved in the design, or conduct, or reporting,  
16  
17 352 or dissemination plans of our research

### 18 19 353 *Protection of the rights and interests of patients*

20  
21 354 Before the start of this trial, research physicians should inform patients of the  
22  
23  
24 355 trial details in writing, including the nature of the clinical trial, the purpose of the trial,  
25  
26 356 the expected benefits and the risks. The researchers are responsible for protecting the  
27  
28 357 privacy of the participating patients. Even if the patients decide to withdraw from the  
29  
30 358 trial at any stage, their medical benefits and rights will not be affected in any way, and  
31  
32 359 they can continue to receive other effective treatment. For possible adverse events, the  
33  
34 360 experiment will also design corresponding solutions. In addition, after the experiment  
35  
36 361 is completed, the patients will be given the results by telephone. Translated written  
37  
38 362 consent is attached as a supplement file (Supplement Materials).

### 39 40 41 42 363 *Dissemination plan*

43  
44 364 The trial findings will be published in peer-reviewed journals and will also be  
45  
46 365 disseminated through presentations at national and/or international conferences.

### 47 48 49 366 *Discussion*

50  
51 367 The optimization of nonoperative management of appendicitis, including the  
52  
53 368 dosage form and duration of antibiotic use, is being actively researched.[15] However,  
54  
55 369 the types of antibiotics used in studies vary, and the selected antibiotics are not  
56  
57 370 common in many regions worldwide, such as low- and middle-level developing  
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3 371 countries. In addition, the role of anti-anaerobic agents in the treatment of  
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5 372 uncomplicated appendicitis remains to be explored and emphasized. These factors  
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8 373 make it difficult for clinicians to choose a reasonable antibiotic regimen for the  
9  
10 374 treatment of appendicitis.

11  
12 375 Some studies showed that only supportive care of uncomPLICATE AA or  
13  
14 376 diverticulitis is noninferior to antibiotics.[16, 33, 34] However, a number of  
15  
16  
17 377 etiological studies have demonstrated that anaerobic bacteria especially  
18  
19 378 *Fusobacterium nucleatum/necrophorum* are a nonnegligible risk factor for acute  
20  
21 379 appendicitis. [23-26] There is currently a lack of a multicenter randomized controlled  
22  
23 380 trial exploring the necessity of anti-anaerobic agents in the NOM of uncomplicated  
24  
25 381 appendicitis.

26  
27  
28 382 According to our previous retrospective study, cephalosporin alone and  
29  
30 383 cephalosporin combined with nitroimidazole are common clinical treatment protocols  
31  
32 384 in China and have similar short-term outcomes in the treatment of uncomplicated AA.  
33  
34 385 However, few studies have compared the long-term outcomes of the different  
35  
36 386 treatment strategies due to the lack of follow-up information after discharge.[20] To  
37  
38 387 our knowledge, to date, no double-blinded randomized controlled trials have  
39  
40 388 compared three generations of cephalosporins combined with three generations of  
41  
42 389 cephalosporins combined with ornidazole in the treatment of uncomplicated AA.  
43  
44 390 Thus, we designed the OPTIMA trial to evaluate the safety and efficacy of a  
45  
46 391 combination of anti-anaerobic agents in the treatment of uncomplicated AA and its  
47  
48 392 prognostic impact. The results of this study are of great significance for guiding  
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50 393 clinical antibiotic use in an environment where antibiotic treatment regimens are not  
51  
52 394 standardized and rational.

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57  
58 395 ***Strengths and limitations of this study***  
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3 396 In this trial, ultrasound, CT and MRI are both chosen as examination techniques  
4  
5 397 for appendicitis, since the accurate distinction between complicated and  
6  
7 398 uncomplicated AA is the key to rational treatment of appendicitis. Considering that  
8  
9 399 CT is not available at night at several nonteaching hospitals, patients with milder  
10  
11 400 conditions may be reluctant to undergo more expensive CT and MRI scans. If we  
12  
13 401 exclude these patients, it might increase the selection bias of the trial due to economic  
14  
15 402 and time factors. The overall sensitivity and specificity are 76% and 95% for  
16  
17 403 ultrasound and 99% and 84% for CT, respectively, and MRI is at least as sensitive  
18  
19 404 and specific as CT.[35-37] Moreover, recent studies have shown that the AIR score  
20  
21 405 has an advantage in diagnosing appendicitis due to its high sensitivity and  
22  
23 406 specificity.[27-32] Therefore, a combination of the AIR score and imaging will be  
24  
25 407 used to diagnose uncomplicated appendicitis in this study. All examination items and  
26  
27 408 results will be stored in a timely manner in the ResMan system, the data will be  
28  
29 409 verified and re-evaluated at any time by the dedicated data management review  
30  
31 410 committee (DMRC), and patients who do not meet the criteria for uncomplicated  
32  
33 411 appendicitis will be excluded. Thus, the diagnosis of noncomplicated AA in this trial  
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35 412 is ensured to be reliable.  
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42 413 In terms of antibiotic selection, ertapenem is a broad-spectrum antibiotic with an  
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44 414 anti-anaerobic effect that has been shown to be effective in the treatment of  
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46 415 appendicitis in previous studies and is recommended in the guidelines.[13] However,  
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48 416 compared with ertapenem, which is expensive and difficult to obtain, the antibiotics  
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50 417 chosen in this study are readily available and safe, which makes the optimized  
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52 418 nonoperative treatment of appendicitis obtained from the experimental results easier  
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54 419 to popularize. In addition, according to previous studies, antibiotic treatment for  
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56 420 uncomplicated acute appendicitis was shown to have the highest recurrence rate  
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3 421 during the first three months after discharge.[6, 7, 9] We speculate that this finding is  
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5 422 related to anaerobic bacteria in the intestinal tract. Thus, we plan to test this by  
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7 423 comparing ceftazidime plus placebo with ceftazidime plus ornidazole for  
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9 424 uncomplicated AA because of the excellent anti-anaerobic activity of  
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11 425 nitroimidazoles.[38-40]  
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15 426 To date, this study has the largest sample size among uncomplicated AA studies  
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17 427 to evaluate the short-term and long-term prognoses. This study not only discusses the  
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19 428 efficacy of combined anti-anaerobic drugs in the treatment of uncomplicated  
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21 429 appendicitis but also focuses on the cure rate and recurrence rate of patients during the  
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23 430 follow-up period after discharge and explores methods for reducing the recurrence  
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25 431 rate of appendicitis.  
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29 432 For uncomplicated AA, it is difficult to obtain bacteriological evidence from the  
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31 433 patient's abdominal cavity. In this study, bacteriological information about AA was  
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33 434 collected only at the time of surgical treatment. Therefore, the anti-anaerobic drugs  
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35 435 were selected based on a 2016 study of clinical characteristics and antimicrobial  
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37 436 patterns in complicated intra-abdominal infections in China.[41] In addition, a 2017  
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39 437 retrospective study of appendicitis treatment reached similar conclusions about  
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41 438 antibiotic use.[20] There were other limitations to this study. We did not set a placebo  
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43 439 group with only supportive care considering the safety and interests of patients. Even  
44  
45 440 though, it is feasible to explore the role of anti-anaerobic agents in uncomplicated  
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47 441 appendicitis. Moreover, a sufficiently large sample and one year of standardized  
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49 442 follow-up are required to investigate the effect of anti-anaerobic drugs on the long-  
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51 443 term outcome of appendicitis. This is a challenge for the subcenters in how to conduct  
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53 444 research operations in an emergency department setting and how to respond promptly  
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55 445 and accurately to emergency problems.  
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6 447 ***Declarations***7  
8 448 **Acknowledgements:** We acknowledge Jingdong Junzhuo Pharmaceutical Co., LTD  
9  
10 449 for providing the study drugs.11  
12 450 **Authors' contributions:** All authors were involved in the study design, and read and  
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15 451 approved the final manuscript. J R, R S and P W contributed to conception and design  
16  
17 452 of this study. J W and H J provided statistical advice. J W, H J, S L and X W are  
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19 453 responsible for contacting with the subcenters. J R, R S, P W, X W and J W are  
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21 454 members of data management review committee. J W and H J drafted the manuscript.22  
23 455 **Competing interests:** Jingdong Junzhuo Pharmaceutical Co., LTD provides the  
24  
25 456 study drugs (ornidazole and sodium chloride injection, ceftazidime injection and  
26  
27 457 simulants) for this investigator-initiated study but has no influence on the study  
28  
29 458 design, data analysis, or report. The investigators take full responsibility for the  
30  
31 459 integrity and content of this paper. And the authors declare that they have no  
32  
33 460 competing interests.34  
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### 573 **Figure legends**

574 Figure 1: OPTIMA flowchart of enrollment, interventions, and follow-up.

575 Abbreviation: ivgtt, intravenous drip; CRP, C reactive protein; VAS, Visual Analog  
576 Scale.

577 Figure 2: Follow-up schedule of OPTIMA. Abbreviation: VAS, Visual Analog Scale.

578 \* Follow-up after discharge can be conducted either by telephone or in an outpatient  
579 clinic as recommended.

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3 580 \*\* If symptoms of suspected appendicitis appear during follow-up after discharge,  
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5 581 relevant examinations should be performed and records should be made.

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7 582 \*\*\* Patients undergoing surgical treatment should be recorded separately including  
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9 583 disease complications and surgical complications as well as their respective adverse  
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11 584 events.  
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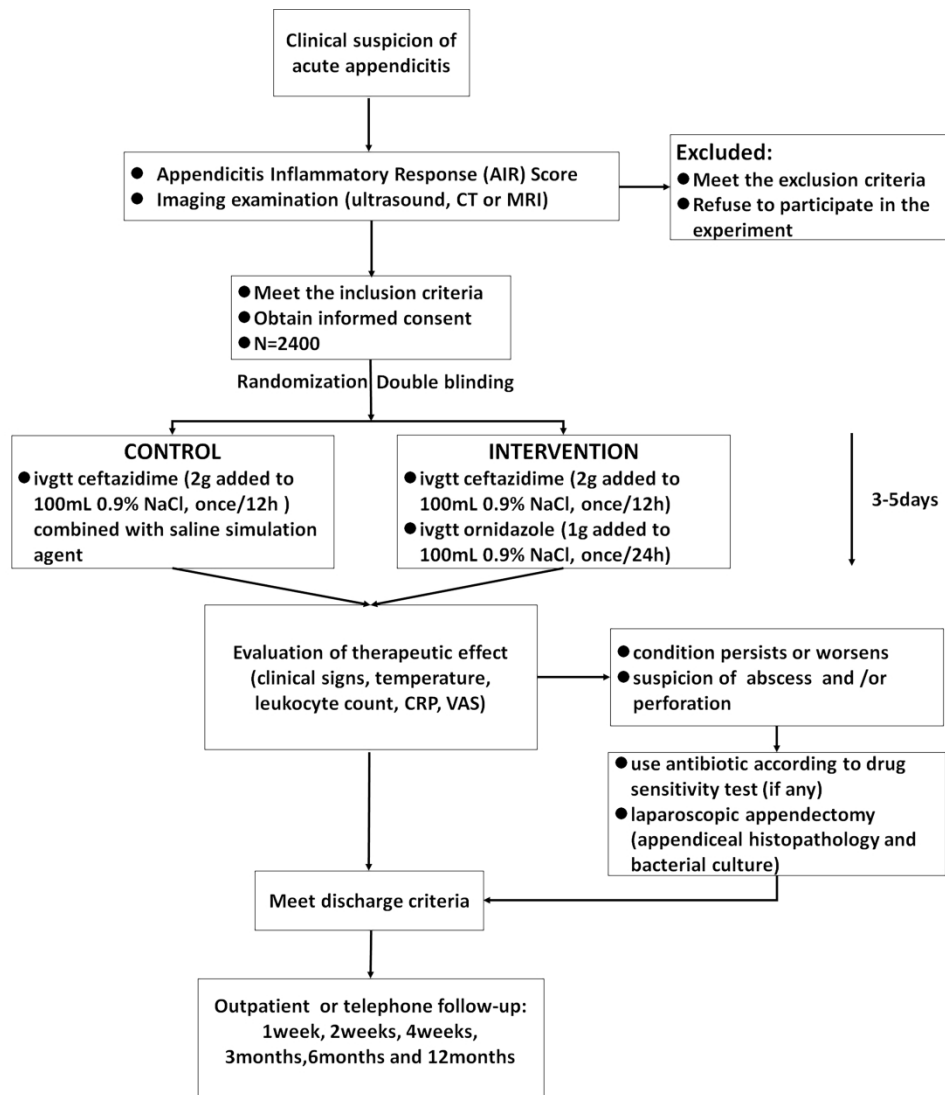


Figure 1: OPTIMA flowchart of enrollment, interventions, and follow-up. Abbreviation: ivgtt, intravenous drip; CRP, C reactive protein; VAS, Visual Analog Scale.

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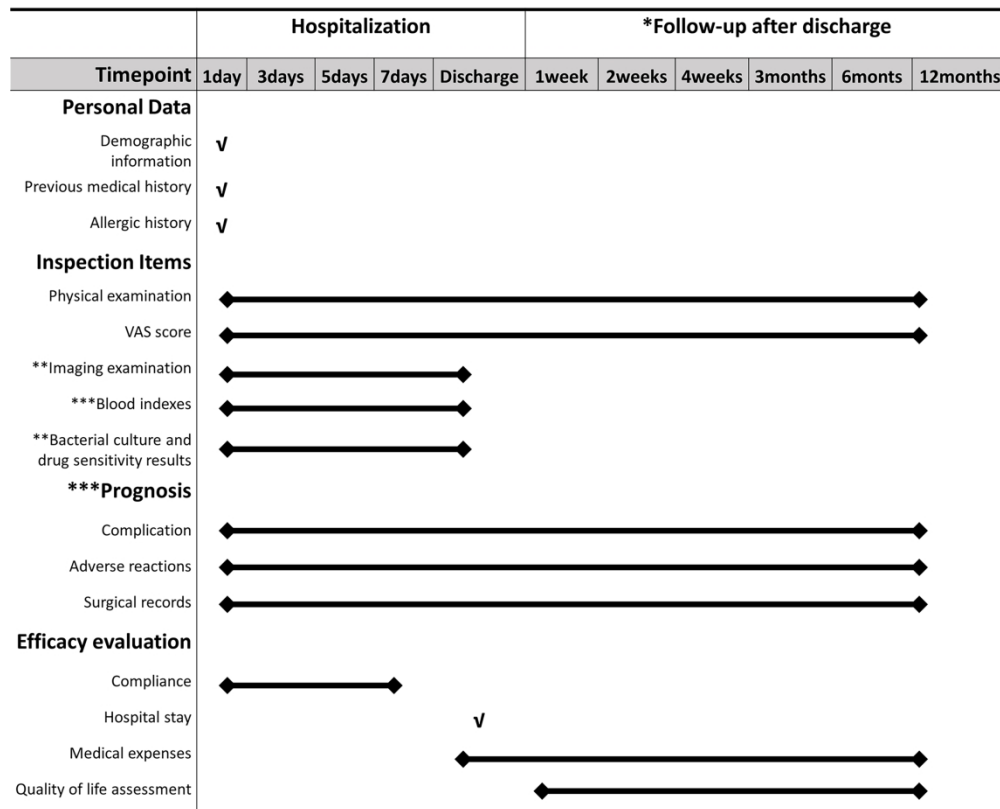


Figure 2: Follow-up schedule of OPTIMA. Abbreviation: VAS, Visual Analog Scale.

\* Follow-up after discharge can be conducted either by telephone or in an outpatient clinic as recommended.

\*\* If symptoms of suspected appendicitis appear during follow-up after discharge, relevant examinations should be performed and records should be made.

\*\*\* Patients undergoing surgical treatment should be recorded separately including disease complications and surgical complications as well as their respective adverse events.

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# CONSENT FORM

## PART I NOTICE TO PATIENTS

Dear patients and families,

We are going to carry out a “Optimizing the treatment for uncomplicated acute appendicitis: a multicentre, randomized double-blinded placebo-controlled study (OPTIMA trial)”. And you may meet the inclusion requirements of this study, therefore, we would like to invite you to participate in this study. We will introduce the purpose, process, benefits and risks of this study to you. Please read it carefully before deciding whether to participate in this study. You are able to ask questions and communicate when your doctor explains and discusses this informed consent. You can make your decision after full discussion with your family, friends and doctor.

If you are currently participating in another clinical study, please inform your doctor.

### WHY IS THIS STUDY BEING DONE?

Acute appendicitis (AA) is one of the most common indications for emergency surgery in the world. In 2019, there were an estimated 17.7 million cases (incidence 228/100,000). Appendectomy was first proposed by Mc Burney in 1894. For more than a century since then, appendectomy has been the golden standard treatment for appendicitis and has been widely applied in clinical practice. Although appendectomy is generally well tolerated, it is a major surgical intervention and can lead to some postoperative complications, such as bleeding, incision infection, adhesion of intestinal obstruction, fecal fistula, appendiceal stump inflammation. Therefore, how to treat acute appendicitis more effectively and safely has aroused the attention of clinicians.

Currently, laparoscopic surgery is widely used in the treatment of acute appendicitis. However, in recent years, more and more international clinical trials have confirmed that non-surgical treatment (conservative treatment) or conservative treatment followed by surgery have better therapeutic effects and lower incidence of complications. Conservative treatment also costs less, but there is a risk of recurrence. According to literature reports, the recurrence rate in Europe and America is 25%-35%. However, the choice of conservative treatment for appendicitis is varied and lack of medication standards. In addition, recent high-quality studies have reported that placebo treatment is as effective as antibiotic treatment for uncomplicated appendicitis in an Asian population.

Therefore, it is urgent for domestic clinicians to promote the standardized treatment of this most common disease in general surgery combined with national conditions and disease characteristics, so as to ensure the maximum efficacy and reduce the consumption of human, material and financial resources of patients.



## WHAT ARE THE OBJECTIVES OF THE STUDY?

To explore the difference in efficacy, complication rate and medical cost between ceftazidime combined with placebo and ceftazidime combined with ornidazole in the treatment of acute uncomplicated appendicitis.

## WHAT KIND OF PARTICIPANTS ARE NEEDED FOR THE STUDY?

2,400 acute appendicitis patients will be enrolled nationwide in accordance with government regulations and relevant institutional policies and procedures. The enrolled patients are eligible for the diagnosis of acute appendicitis, aged between 18 and 65 years old, and have no allergic reaction to the treatment drugs involved, no history of acute or chronic appendicitis, no liver or kidney dysfunction, sepsis and other symptoms. Female patients who are pregnant, in lactation or planning pregnancy will be excluded.

## STUDY PROCEDURE AND FOLLOW-UP SCHEDULE?

The study will be conducted by 80 centers nationwide, with 2,400 cases planned to be collected, led by the General Hospital of Eastern Theater Command. During the period of your participation in this clinical study, your doctor will collect your health information periodically to evaluate the effect of this treatment from the date of formal enrollment to 1 year after the end of your treatment.

We will assign you to ceftazidime combined with ornidazole or ceftazidime combined with placebo for no more than 7 days after you agree to enroll. The doctor will evaluate treatment effect at any time, take the effectiveness and safety of treatment as the first consideration, and perform surgical treatment for you if the conservative treatment effect is not ideal.

During the study period, you should not take any medications other than those prescribed or permitted by your study physician. For your safety and to ensure the effectiveness of the study, you should not participate in any other clinical studies involving drugs and medical devices during this period. Use effective contraceptive methods throughout the study period up to 2 weeks after treatment.

We will follow you up 1 day before treatment and 1 day, 3 days, 5 days, 7 days, 1 week, 2 weeks, 1 month, 3 months, half a year and 1 year after treatment according to your treatment status. The follow-up will cover your daily health status, discomfort and treatment-related complications. All measures based on your situation are required

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3 instead of additional examinations. If there is no need for further hospitalization, the  
4 follow-up after your treatment can be conducted by phone, outpatient service or  
5 WeChat, etc. Please confirm that you can cooperate with the doctor for follow-up within  
6 the specified follow-up time.  
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## 10 **ARE THERE BENEFITS TO TAKING PART IN THE STUDY?**

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Regardless of which group you are in, all ceftazidime and ornidazole used for your participation in this study will be provided free of charge, including ceftazidime and ornidazole used if conservative treatment fails and surgical treatment is required. However, the expenses related to other diseases shall be borne by you. Your doctor will closely observe you after your treatment and follow you up for at least 1 year, which will help to detect and treat any health problems during your follow-up. In the research process, professional doctors will do disease diagnosis, disease tracking observation, treatment guidance and disease consultation for you. The tests required to confirm your diagnosis, determine the extent of your disease, and assess the effect of your treatment are normal medical examinations, and this study will not add to your burden in this regard.

All drugs involved in this study have been approved in China for the treatment of patients with conditions similar to or even worse than yours. The information obtained from this study will help us develop a more reasonable, comprehensive and reliable diagnosis and treatment path and treatment norms for this disease, and promote it in patients with similar conditions to yours.

If the adverse reactions occurred during the study period due to the use of the study drugs need to be treated, the relevant expenses shall be covered by the company that provides drugs. If the adverse reactions are caused by medical negligence, the relevant expenses shall be borne by the relevant hospitals.

## WHAT ARE THE RISKS OF THE STUDY?

### **Recurrence**

Antimicrobial drugs can save you from surgical injury, but there is a certain risk of recurrence. According to the team's preliminary research results, the recurrence rate is 19% in Chinese population and 25%-35% in European and American population. But studies have shown that surgery after recurrence does not have a higher complication rate than surgery directly.

## Transferring to surgery

Conservative treatment of acute appendicitis may still require surgical treatment. However, according to existing reports, reoperation after the failure of conservative treatment does not increase the incidence of surgical complications.

## Adverse drug reaction

All drugs involved in this study have been extensively validated for safety and efficacy and have been approved for marketing by CFDA in China. But no drug is completely safe. During the treatment, you may not have any adverse reactions, or some drug-related adverse reactions may occur, but the adverse reactions mentioned in the study can be basically recovered after withdrawal.

According to the description in the drug instructions, the adverse reactions of the various drugs to be used in this study are as follows:

Ornidazole is generally well tolerated and the following reactions may occur during administration: 1. Digestive system: including mild stomach discomfort, nausea, bad breath, etc. 2. Nervous system: including dizziness and drowsiness, vertigo, etc.; 3. Irritation: rash, itchy, etc. 4. Others: leukopenia and so on

The adverse reactions of ceftazidime are rare and mild. A few patients may have skin rash, itching, drug fever; Nausea, diarrhea, abdominal pain; Mild phlebitis at the injection site; Occasionally transient elevation of serum aminotransferase, blood urea nitrogen and blood creatinine can occur. Leukopenia, thrombocytopenia and eosinophilia.

Your doctor and nurse will monitor your reaction at all times. If you experience any discomfort during the trial, you should inform your doctor at any time. Your doctor will give you other medications to relieve the discomfort. If you or your doctor determines that you cannot tolerate it, the study drug will be completely discontinued and you may be withdrawn from the study.

In addition to the risks of drugs, there are some related risks such as:

## Imaging examination

You will be exposed to a minuscule amount of radiation during the CT examination, but these are necessary for routine diagnosis and evaluation.

## Draw blood for examinations

The risks of taking blood from your arm include temporary discomfort and/or bruising. Infection, excessive bleeding, clotting, or fainting may occur, but they are highly unlikely.

## Operation

Any operation may have surgical complications, and appendectomy in this project may cause bleeding, incision infection, adhesive intestinal obstruction, fecal fistula, appendicitis, etc.

## WHAT ARE YOUR RIGHTS AS A PARTICIPANT?

You can choose not to participate in this study, which will have no adverse impact on your access to conventional treatment.

After you agree to participate in the study, you can change your mind at any time and tell the investigator to withdraw from the study in time. Your withdrawal will not affect your access to regular medical services. After the study is completed or discontinued, you will no longer be provided with the drugs in the study program free of charge.

## COMPENSATION?

Please inform your responsible investigator of any study related injury to your health during your participation in this study and provide your contact number \_\_\_\_\_. We will take the necessary medical measures. According to China's relevant laws and regulations, in case of irreversible injury related to the study, the person in charge of this study will deal with and treat it in time and provide corresponding economic compensation.

If you have questions related to the rights and interests of patients, you may contact the clinical trial ethics committee of your hospital at: \_\_\_\_\_.

## WHAT ABOUT CONFIDENTIALITY?

Your participation and personal data in the study are confidential. All study members and sponsors are required to keep your identity confidential. No personal information about you will be disclosed when the results of this study are published.

## PART II STATEMENT OF CONSENT AND AUTHORIZATION

### Patient informed consent Statement:

I have been informed of the research background, purpose, procedure, risks, benefits and rights of “Optimizing the treatment for uncomplicated acute appendicitis: a multicentre, randomized double-blinded placebo-controlled study (OPTIMA trial)”. I have ample time and opportunity to ask questions and I am satisfied with the answers. I am also told who to contact when I have questions or want further information. I have read this informed consent and agree to participate in this study. I know that during the study I can withdraw from the study at any point without any reason. I am told that I will get a copy of the informed consent, which contains my signature and that of the researcher.

Patient Signature:

Date:

Signature of Legal Representative [if applicable]:

Date:

Relationship with Patient:

When the patient or his/her legal representative is unable to read or write, at least one impartial witness must be present to confirm that the information in the informed consent has been correctly interpreted and that the patient and/or the subject's legal representative have understood the information. The patient voluntarily agreed to participate in the study.

Fair Witness Signature:

Date:

### Statement from the researchers

I have informed the patient (and his/her legal representative) of the background, objectives, procedures, risks, and benefits of the “Optimizing the treatment for uncomplicated acute appendicitis: a multicentre, randomized double-blinded placebo-controlled study (OPTIMA trial)”, and have given him/her sufficient time to read the informed consent, discuss with others, and answer his/her questions about the study; I have informed the patient of the contact information in case of problems; I have advised the patient (or legal representative) that he/she may withdraw from the study at any time during the study period without any reason.

Signature of Researchers:

Date:



STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description	Addressed on page number
<b>Administrative information</b>			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	P1/L1-3
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	P3/L53
	2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	3	Date and version identifier	
Funding	4	Sources and types of financial, material, and other support	P19/L460-462
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	P1/L4-L22
	5b	Name and contact information for the trial sponsor	P1/L13-20
	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	P18/L455-459
	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)	P14/L341

1	<b>Introduction</b>			
2				
3	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	P4/L70-133
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6		6b	Explanation for choice of comparators	P9/L219-221
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8	Objectives	7	Specific objectives or hypotheses	P5/L112-113
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10	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)	P5/L121-128
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14	<b>Methods: Participants, interventions, and outcomes</b>			
15				
16	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	P6/L130
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19	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)	P6/L148-170 P11/L260-266
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23	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	P10/L222-242
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26		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)	P10/L236-242
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29		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	P11/L252-256
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32		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	P10/L236-242
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34	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	P11/L268-292
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40	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)	P6/L121-128
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1	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	P8/L197-217
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4	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	P10/L219-221
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6	<b>Methods: Assignment of interventions (for controlled trials)</b>			
7	<b>Allocation:</b>			
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10	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	P7/L172-186
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16	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	P8/L188-195
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20	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	P8/L183
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24	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	P8/L183,188-195
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27		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	P14/L333-336
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31	<b>Methods: Data collection, management, and analysis</b>			
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33	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	P13/L320-331
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39		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	P11/L250-256
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1	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	P12/L295-306
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5	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	P13/308-331
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8		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	P13/L308-319
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10		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	P13/L310-312
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14	<b>Methods: Monitoring</b>			
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16	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	P14/L340-341
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22		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	P14/L341-343
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25	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	P12/L287-290
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28	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	P14/L341-343
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32	<b>Ethics and dissemination</b>			
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34	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	P14/L346-349
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37	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)	Not applicable
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1	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	P15/L354-362
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4		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Detail in informed consent form
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8	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	Detail in informed consent form
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13	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	P18/L455-459
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16	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	P19/L463-468
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19	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	Detail in informed consent form
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24	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, health care professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	P15/L364-365
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28		31b	Authorship eligibility guidelines and any intended use of professional writers	Not applicable
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30		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Not applicable
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33	<b>Appendices</b>			
34	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	See supplement materials
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39	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	Not applicable
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\*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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