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

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Abstract

Introduction Acute appendicitis (AA) is one of the most common surgical emergencies. An increasing number of studies prove that antibiotics are non-inferior to appendectomy in patients with uncomplicated AA. Recently, a Korean open-label study has been demonstrated that no benefit from antibiotics compared with symptomatic treatment of uncomplicated AA. Meanwhile, the APPAC III trial has been conducting to compare the role of antibiotic therapy with placebo in the treatment CT scan-confirmed uncomplicated AA. The latest guidelines from WSES recommend antibiotics as a safe alternative to surgery in uncomplicated AA. However, there is no consensus regarding the optimum regimens, a double-blinded placebo-controlled study to illustrate the role of antibiotics of uncomplicated AA is still lacking.

Methods and analysis: The OPTIMA trial is a multicentre, double-blind, placebo-controlled, superiority randomized study aiming to evaluate the role of anti-anaerobic bacteria antibiotics in the resolution of uncomplicated AA. Patients (aged 18-65 years) diagnosed with uncomplicated AA (without gangrenous and/or perforated appendicitis or appendiceal abscess or appendiceal fecalith) are qualified for inclusion. Totally, 2400 eligible subjects will participate in the experiment. The primary endpoint of this study is success rate of the treatment, defined as 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 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

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Mann Whitney U test, Chi-square test, as appropriate, a P-value < 0.05 is considered significant.

Ethics and dissemination: The protocol has acquired the approve of the Ethics Committee of Jinling Hospital on November 13, 2018(2018NZKY-027-01). The trial findings will be published in peer-reviewed journals.

Trial registration: Chinese Clinical Trial Register, ChiCTR1800018896

Strengths and limitations of this study

Strength 1: To our knowledge, OPTIMA is the first multicentre, randomized, double-blinded, placebo-controlled clinical study comparing ceftazidime combined with ornidazole versus ceftazidime combined with placebo for uncomplicated acute appendicitis to investigate the role of anti-anaerobic drugs in the conservative treatment of appendicitis.

Strength 2: Multicentre research to ensure that the materials collected are more symbolic. The sub-centers keep the original data, and the data engineers organize and check the data in each center to reduce the errors in the data collection process.

Strength 3: Ceftazidime and ornidazole are widely used in the treatment of appendicitis due to their low cost and easy availability, which means the optimized non-surgical treatment of appendicitis obtained from the experimental results is easier to popularize.

Limitation 1: For acute uncomplicated appendicitis, physicians need to make a timely and accurate diagnose and then get informed consent from the patient, to estimate the patients whether meets the uncomplicated diagnosis without surgical pathology remains a challenge for surgeons.

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Limitation 2: Since the treatment of uncomplicated appendicitis in this study is antibiotics alone, we cannot acquire the results of surgical pathology and bacteriological analysis, only when they need surgical intervention.

Introduction

Acute appendicitis (AA) is one of the most common indications for emergency surgery in the world.[1] In 2019, there were an estimated 17.7 million cases (incidence 228/100,000).[2] Appendectomy was first proposed by Mc Burney in 1894[3]. 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 be associated with postoperative morbidity.

AA can be classified as either simple or complex. The latter includes gangrenous and/or perforated appendicitis as well as any appendicitis with intra-abdominal or pelvic abscess (IAA).[4] In recent years, the treatment of AA has been under active debate and discourse that an increasing amount of evidence has shown that the majority of patients with uncomplicated acute appendicitis can be treated with antibiotics alone instead of surgery.[5-10] Therefore, the guidelines recommend antibiotic treatment for uncomplicated AA when the patients accept the recurrence risk.[11]

At present, there is no consensus on the choice of antibiotics and different antibiotic regimens are adopted. A five-year follow-up study of antibiotic therapy for uncomplicated AA from Finland adopted antibiotic therapy with intravenous ertapenem for 3 days followed by 7 days of oral levofloxacin and metronidazole. And the study showed that antibiotic therapy is non-inferior to appendectomy.[8]

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However, the antibiotics in this trial are not the preferred choice in China. According to our previous study, intravenous three generations of cephalosporins with or without nitroimidazoles are the most common regimens, and the success rate was similar.[12]But the usage of antimicrobial drug regimens in conservative treatment for AA lacks standardization and rationality. Additionally, in other trials or guidelines, the usage of antibiotics regimen is also various, which will bring confusion for physicians in the choice of AA conservative treatment.

Additionally, some studies have shown no benefit of antibiotic therapy in uncomplicated acute diverticulitis, which results in trials to be designed and conducted aiming to prove the no benefit of antibiotic therapy also in AA. Thus, whether to use antibiotics and which regimen to choose need more clinical trials to prove.

The APPAC group designed and published a protocol which is a multicentre, double-blind, placebo-controlled, superiority randomized study comparing antibiotic therapy with placebo in the treatment CT scan-confirmed uncomplicated acute appendicitis aiming to evaluate the role of antibiotics in the resolution of uncomplicated acute appendicitis. Recently, Park et al reported results regarding possible spontaneous resolution in uncomplicated acute appendicitis. But their study was single-blind (participants only), not double-blind. Moreover, the recurrence of appendicitis in the no-antibiotic group has a higher tendency than the antibiotic group, although they did not detect statistical differences which maybe because of the small sample size.[13]

On the other hand, cephalosporins combined with nitroimidazoles as the preoperative prophylactic antibiotic regimens have been proved that this combination can reduce the incidence of surgical site infection compared with cephalosporins

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alone, no matter in non-complicated or complicated AA patients.[14]A prospective randomized double-blinded randomized controlled trial also revealed a significant decrease in wound infection rates by giving 2 postoperative intravenous doses of antibiotics, suggesting postoperative antibiotics are of benefit in simple appendicitis.[15]Accordingly, we inferred that antibiotic regimens have the effects on decreasing recurrence of AA, especially in combination with anti-anaerobes drugs regimens.

Bacterial resistance has been a global issue. It is increasingly worthwhile to develop rational antibiotic treatment strategies.[16] This study aims to evaluate the therapeutic efficiency of the anti-anaerobes covered strategy as compared to anti-anaerobic uncovered regimens in uncomplicated AA, providing a reference for rational antibiotic selection. To our knowledge, so far, no double-blinded randomized controlled trials are comparing three generations of cephalosporins combined placebo with three generations of cephalosporins combined ornidazole in the treatment of uncomplicated AA.

Methods

Trial design

The OPTIMA trial is a multicentre, randomized, double-blind, parallel controlled clinical trial to evaluate the therapeutic qualities and efficiency of a combined anti-anaerobes strategy comparing with no anti-anaerobic agents. In each center, patients are randomly allocated to the experimental treatment arm (intravenously administer ceftazidime combined with ornidazole) or the control arm (intravenously ceftazidime combined with saline simulation agent) in an equal ratio of 1:1. Figure 1 reveals the enrolment, interventions, and follow-up of participants in two conservative treatments for acute appendicitis.

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Trial setting

The trial will take place in 80 hospitals in China. All participating hospitals will recruit a specified number of patients according to the annual admission volume of each center. In all participated hospitals appendectomy is mostly performed laparoscopically.

Eligibility criteria and procedures

Patients aged 18 to 65 who are suspected clinical manifestations of acute appendicitis will be allowed to take part in the study. Clinical symptoms, signs, and laboratory tests including blood routine, C reactive protein (CRP), creatinine, and female human chorionic gonadotropin HCG) are evaluated by the surgeon. And patients must have imaging tests to further diagnosis when patients have at least two of the following signs: white blood cell count $>10\times10^9$/L, axillary temperature> 38.5℃, C reactive protein (CRP)>10mg/L, acute right lower abdominal pain (including metastatic or persistent right lower abdominal pain), tenderness and rebound pain. If an uncomplicated AA is diagnosed by imaging (ultrasound, CT, or MRI), patients are qualified to be included. Patients or their authorized family members must agree to participate in this study and have signed a written consent form.

Exclusion criteria:

1.Exist complications such as abscess, appendiceal fecalith, or perforation

2. Appendiceal tumor and/or appendiceal soft tissue mass

3. History of acute or chronic appendicitis

4. Suspicion of severe sepsis

5. Patients with a known history of allergy or other contraindication to the study antibiotics

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6. Patients with pre-existing Immunocompromised

7. Patients undergoing other antibiotics treatments

8. Alcoholics

9. Women who are pregnant or plan to be pregnant or breastfeeding within 3 months

10. Refused to sign the informed consent

Allocation and randomisation

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

Blinding

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

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patients are all not known the treatment packages until finishing the study and the data has been locked.

Follow-up will be conducted by the surgeon at each center either by telephone or outpatient. The surgeon who participated in the follow-up is not aware of the patient's previous antibiotic regimen and only records as required on the follow-up form.

Sample size calculation

Given the results of previous studies that antibiotics have a success rate of about 75% in treating uncomplicated appendicitis and the recurrence rate within one year is 25-35% and the recurrence rate of antibiotic treatment for appendicitis is highest within three months after discharge,[5, 17-19] we estimate that the success rate of the combination of anti-anaerobic drugs can increase the cure rate from 75% to 80%. In this condition, we calculated that a minimum of 1091 patients required for each group would achieve a power of 0.8(1-β) and one-sided significance level (α) of 0.025 to conclude the efficacy of the intervention arm is superior to the control arm in the long-terms of cure rate.

In addition, some relevant studies chose the short-term efficacy as the primary outcome in consideration that AA is an acute phase disease and the antibiotics will not have effects on subjects after drug metabolism. So, they make the response rate after a course of drug therapy be the primary outcome. In this condition, we projected sample size of 564 participants for each group with 90% power at a two-sided alpha level of 0.05 using the PASS software (PASS 11, NCSS software, Kaysville, USA) to conclude the efficacy of the intervention arm is superior to the control arm (from 96% to 99%).

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Therefore, to be sufficient to analyze both the short- and long-term efficacy of antibiotic therapy, we chose the first algorithm for sample size estimation, and a total of 2400 patients, with an estimated dropout rate of 10% total of patients.

Recruitment plan

Recruitment of participants will start in January 2022 and follow-ups should be carried out at the same time. All 2400 patients are expected to be enrolled by the end of 2022.

Interventions

Antibiotic use protocol

Patients are randomly assigned in an equal ratio of 1:1 to accept either the experimental treatment arm (intravenously administer ceftazidime combined with ornidazole) or the control arm (intravenously ceftazidime combined with ornidazole simulation agent). The experimental treatment group: Ceftazidime (2g added to 100mL 0.9% NaCl injection for intravenous drip, once/12h) + Ornidazole (1g added to 100mL 0.9% NaCl injection for intravenous drip, once/24h) for 3-5d of routine treatment. The control group: ceftazidime (2g added to 100mL 0.9% NaCl injection for intravenous drip, once/12h) + simulation agent (two doses added to 100mL 0.9% NaCl injection for intravenous drip, once/12h) for 3-5d of routine treatment. In both groups, the maximum extension is not more than 7d depending on the treatment response.

Criteria for transferring to other treatment

In case of a confirmed source of infection through the drug sensitivity test, it is allowed to adopted appropriate antimicrobial agents. If conservative treatment for 24h is not effective or the patient's condition worsened, the treatment strategies should be switched immediately. When suspected an exacerbation of the infection, or the

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occurrence of perforated appendicitis or diffuse peritonitis, patients will undergo an emergency laparoscopic appendectomy and undergo appendiceal histopathology and bacterial culture.

Discharge and follow-up

Patients meeting the clinical cure criteria will be discharged, which means the following criteria must be met at the same time: body temperature (underarm) <37.5℃, white blood cell count $<10.0\times10^9$/L, neutrophil percentage <70%, and no deep tenderness, mass or rebound pain in the right lower abdomen of the subjects during follow- up after the medication. According to the time of conservative treatment, the hospitalization follow-up time is set to 1 week. And the following indicators will be collected on day1,3,5,7: physical examination including Visual Analog Scale (VAS), auxiliary examination, therapeutic effect, surgery status (if any). An outpatient follow-up visit is recommended one week after discharge. Standard follow-up of 2 weeks, 1 month, 3 months, 6 months, and 1 year will be performed by the surgeon either by telephone or in an outpatient setting. For patients treated surgically, follow-up should include the assessment of surgical site infection (SSI) in a month.

If the patient is treated conservatively or surgically for recurrent appendicitis after discharge, the time and contents of treatment should be recorded.

Preparation before implementation

Before the commencement of the clinical trial, training on the trial protocol will be conducted by the head of each trial center to the investigators. Each investigator should understand the content of this clinical trial protocol and master the standard methods of enrollment, recording, and judgment criteria according to Standard Operating Procedure (SOP) and Good Clinical Practice (GCP) guidelines. All

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participated surgeons and residents ought to accept standard train about unified assessment methods of classified different types of AA.

Outcome measures

Primary outcome measure

The primary endpoint of this study is to evaluate the efficiency and long-term outcome of ceftazidime combined with ornidazole, compared with ceftazidime combined with placebo. It is hypothesized that ceftazidime combined with ornidazole is superior to ceftazidime combined with placebo and will increase the one-year cure rate. The conservative treatment success is defined without a change of antibiotics protocol, without the need for surgical intervention or recurrence of appendicitis for at least one year.

Secondary outcome measures

Secondary endpoints are to evaluate the total length of hospital stay; total expenses during the hospitalization; mortality; duration of antibiotic treatment; complications rate; time to fulfill discharge criteria; Pain score (VAS); the use of analgesics; Quality of life assessment (SF-12); readmission rate; percentage of patients requiring appendectomy during initial antibiotic therapy; the number of days absent. Complications will be classified according to conservative treatment or surgery. The former includes antibiotic-related adverse reactions. The latter mainly includes incidence of surgical site infection (SSI), incisional hernia, anastomotic fistula, abdominal abscess, adhesions. The details of data collection were shown in figure 2.

Management and analysis of data

Data collection and management

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The data managers of the statistical unit are responsible for the data management. In each sub-center, the complete raw information of patients will be stored in electronic medical records and paper medical records in order to facilitate later review. Baseline demographics, as well as the related variables of antibiotic treatment and surgery, will be recorded independently by two data administrators. All variables that need to be counted are provided in the full study protocol. These variables should be registered in case report forms (CRFs) which will be entered into ResMan, an electronic data collection and management system supported by the Chinese Clinical Trial Registry. Data will be encrypted and can only be processed with the authorization of the data managers. A Detail Response Questionnaire (DRQ) will be used by the data managers to recorded missing and wrong data. And then the investigator will check the raw materials kept by the hospital.

Statistical analysis

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

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

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All statistical analyses are performed by SAS 9.1 system programming. All statistical tests, except for the superiority test (a one-sided test) of the primary measures, are conducted on a bilateral basis. Continuous variables are described by mean, standard deviation, median, and upper and lower quartiles. Categorical variables are described by frequency and proportion. The one-sided 97.5% CI for proportion difference will be calculated to evaluate the treatment difference (one-sided test at α=0.025). The secondary outcomes will be analyzed using different statistical methods according to the types of data. The t-test or Wilcoxon rank sum test is usually used to compare continuous variables between two groups, and the Chi-square test or Fisher's exact probability test is usually used to compare categorical variables. P-values less than 0.05 will be considered statistically significant for all secondary outcome analyses.

Safety and data monitoring

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

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

Ethics and dissemination

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Ethics

The protocol has acquired the approval of the Ethics Committee of Jinling Hospital on November 13, 2018(2018NZKY-027-01). This trial will be conducted following the Helsinki Declaration and the relevant Chinese clinical trial research norms and regulations.

Patient and Public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research

Protection of the rights and interests of patients

Before the start of this trial, research physicians should inform patients of the trial details in writing, such as the nature of the clinical trial, the purpose of the trial, the expected benefits and the risks. Meanwhile, researchers are responsible to protect the privacy of participated patients. Despite they decide to withdraw from the trial at any stage, their medical benefits and rights will not be affected in any way, and they can continue to receive other effective treatment. For possible adverse events, the experiment also set up corresponding solutions. In addition, after the experiment completed, the patients are given the results by telephone.

Dissemination plan

The trial findings will be published in peer-reviewed journals and will also be disseminated through presentations at national and/or international conferences.

Discussion

The optimization of non-operative management of appendicitis is under active research including the dosage form and duration of antibiotics use.[19, 20] However, the types of antibiotics used in studies are various and the antibiotics they chose are not common in most areas worldwide, like low and middle developing countries. In

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addition, the role of anti-anaerobic agents in the treatment of uncomplicated appendicitis remains to be explored and emphasized. These make it difficult for clinicians to choose a reasonable antibiotic regimen for the treatment of appendicitis.

According to our previous retrospective study, cephalosporin alone and cephalosporin combined with nitroimidazole are common clinical treatment protocols in China and had similar short-term outcomes in the treatment of uncomplicated AA. However, there are few studies comparing the long-term outcomes of the different treatment strategies due to the lack of follow-up information after discharge.[12] To our knowledge, so far, no double-blinded randomized controlled trials are comparing three generations of cephalosporins combined simulation with three generations of cephalosporins combined ornidazole in the treatment of uncomplicated AA. Thus, we design the OPTIMA trial to evaluate the safety and efficacy of combined anti-anaerobic agents in the treatment and prognostic impact of uncomplicated AA. The results of this study are of great significance for guiding clinical antibiotics use in an environment where antibiotic treatment regimens are not standardized and rational.

Strengths and limitations of this study

In this trial, ultrasound, CT and MRI are all chosing as examination techniques for appendicitis, since the accurate distinction between complicated and uncomplicated AA is the key to rational treatment of appendicitis. Considering that CT is not available at night in several non-teaching hospitals, and patients with milder conditions may be reluctant to undergo more expensive CT and MRI scans. If we exclude these patients, it might increase the selective bias of the trial due to economic and time factors. Additionally, several studies have demonstrated the usefulness of ultrasound and Alvarado scoring systems in diagnosing appendicitis in recent years.[21-24] The overall sensitivity and specificity of ultrasound is 76% and 95%,

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for CT is 99% and 84% respectively, and MRI is at least as sensitive and specific as CT.[25-27]Moreover, all examination items and results will be stored timely in the ResMan system, the data will be checked and re-evaluated anytime by the dedicated data management review committee (DMRC) and the patients who do not meet the criteria for uncomplicated appendicitis will be excluded. Thus, the diagnosis of non-complicated AA in this trial is ensured to be reliable.

In terms of antibiotics selection, ertapenem is a broad-spectrum antibiotic with anti-anaerobic effect that has been shown to be effective in the treatment of appendicitis in previous studies and is recommended in the guidelines.[11]However, compared with ertapenem which is expensive and difficult to obtain, the antibiotics chose in this study are readily available and safe, which makes the optimized non-operative treatment of appendicitis obtained from the experimental results is easier to popularize. In addition, according to the previous studies, antibiotic treatment for uncomplicated acute appendicitis had the highest recurrence rate during the first three months after discharge.[5, 19] We speculated that it is related to anaerobic bacteria in the intestinal tract. Thus, we plan to test this by comparing ceftazidime plus simulation with ceftazidime plus ornidazole for uncomplicated AA because of the excellent anti-anaerobic activity of nitroimidazoles.

Up to now, this study is the largest sample size in uncomplicated AA studies, so to be able to evaluate the short-term and long-term prognosis. This study not only discussed the efficacy of combined anti-anaerobic drugs in the treatment of uncomplicated appendicitis but also focused on the cure rate and recurrence rate of patients in the follow-up after discharge and explored the methods to reduce the recurrence rate of appendicitis.

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For uncomplicated AA, it's difficult to get bacteriological evidence from the patient's abdominal cavity. Therefore, the anti-anaerobic drugs are selected based on a 2016 study of clinical characteristics and antimicrobial patterns in complicated intra-abdominal infections in China. In addition, a 2017 retrospective study of appendicitis treatment reached similar conclusions about antibiotic use.[28] Besides, a sufficiently large sample and one year of standardized follow-up are required to investigate the effect of anti-anaerobic drugs on the long-term outcome of appendicitis. This is a challenge for the sub-centers in how to conduct research operations in an emergency department setting and how to respond promptly and accurately to emergent problems.

Conclusion

The OPTIMA trial is a multicentre, double-blind, placebo-controlled, superiority randomized study aiming to evaluate the role of anti-anaerobic bacteria antibiotics in the resolution of uncomplicated AA.

Declarations

Acknowledgements: We acknowledge Jingdong Junzhuo Pharmaceutical Co., LTD for providing the study drugs.

Authors' contributions: All authors were involved in the study design, and read and approved the final manuscript.

Competing interests: Jingdong Junzhuo Pharmaceutical Co., LTD provides the study drugs (ornidazole and sodium chloride injection, ceftazidime injection and simulants) for this investigator-initiated study but has no influence on the study design, data analysis, or report. The investigators take full responsibility for the

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integrity and content of this paper. And the authors declare that they have no competing interests.

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Figure legends

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

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

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.

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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.

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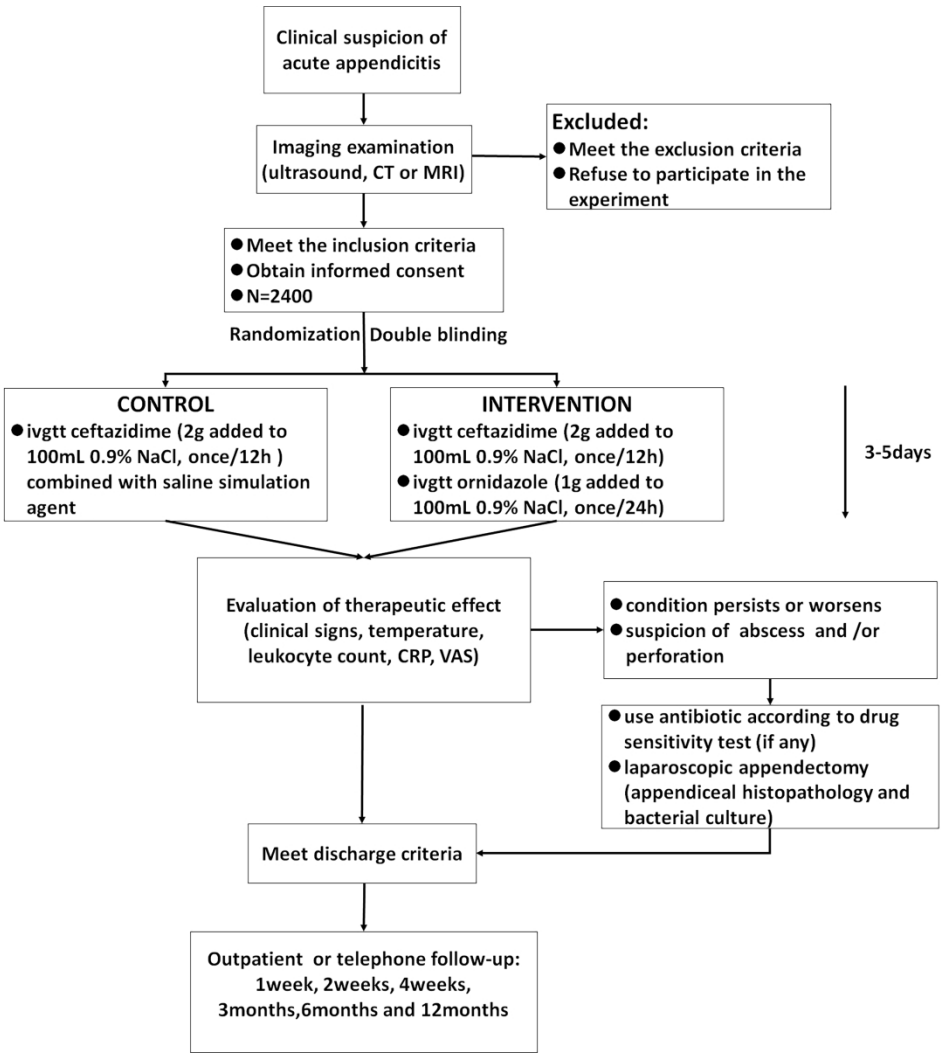

Figure 1: OPTIMA flowchart of enrollment, interventions, and follow-up. Abbreviation: ivgtt, intravenous drip; CRP, C reactive protein; VAS, Visual Analog Scale.

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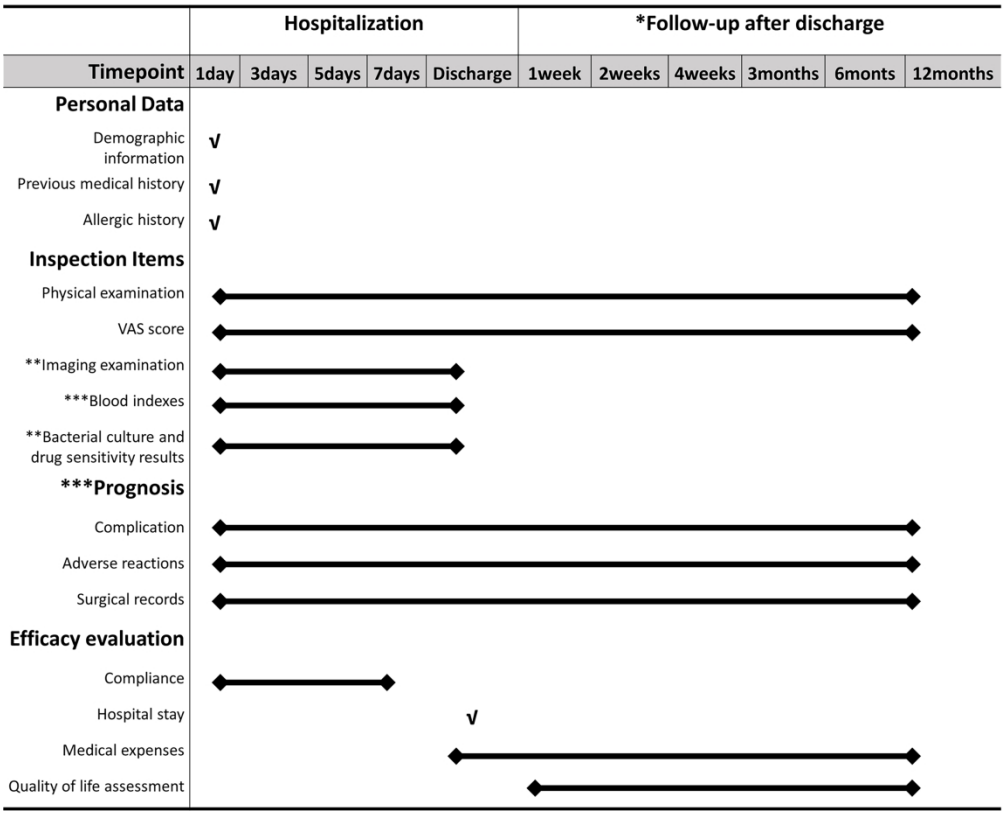

Figure 2: Follow-up schedule of OPTIMA. Abbreviation: VAS, Visual Analog Scale.
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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
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

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Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	P4/L76-135
	6b	Explanation for choice of comparators	P6/L128-135
Objectives	7	Specific objectives or hypotheses	P6/L125-127
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)	P6/L138-140
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	P6/L147
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)	P7/L152-176 P11/L265-271
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	P10/L228-239
	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/L241-247
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	P11/L254-259
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	P10/l229-232
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	P12/L274-290
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/L138-145

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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
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	P10/L224-226
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	P8/L178-192
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
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	P8/L178
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
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	P14/L332-335
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	P11/L253-261
	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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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
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
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	P13/L312-318
	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
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	P14/L339-340
	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	
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
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
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	P14/L345-346
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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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
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Detail in informed consent form
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
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	P18/L440-441
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
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
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	P15/L362-363
	31b	Authorship eligibility guidelines and any intended use of professional writers	Not applicable
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Not applicable
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	See supplement materials
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" license.

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

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

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Abstract

Introduction Emerging evidence has shown that an antibiotics-first strategy is a 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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Ethics and dissemination: The protocol has acquired the approve of the Ethics Committee of Jinling Hospital on November 13, 2018(2018NZKY-027-01). The trial findings will be published in peer-reviewed journals.

Trial registration: Chinese Clinical Trial Register, ChiCTR1800018896

Strengths and limitations of this study

Strength 1: The OPTIMA trial is the first multicenter, randomized, double-blinded, placebo-controlled clinical study comparing ceftazidime combined with ornidazole versus ceftazidime combined with placebo for uncomplicated acute appendicitis to investigate the role of anti-anaerobic drugs in the conservative treatment of appendicitis.

Strength 2: A double-blinded trial with a placebo can reduce bias and confirm the role of anti-anaerobic agents in the treatment of appendicitis.

Strength 3: The data will be collected and saved in an electronic data capture system (EDC) to guarantee the integrity of the data, and the data engineers will organize and check the data from each center to reduce errors in the data collection process.

Limitation 1: Since the treatment of uncomplicated appendicitis in this study involves antibiotics alone, we cannot collect data on surgical pathology and bacteriological analysis, unless surgical intervention is required.

Introduction

Acute appendicitis (AA) is one of the most common indications for emergency surgery worldwide.[1] In 2019, there were an estimated 17.7 million cases (incidence, 228/100,000).[2] Appendectomy was first proposed by Mc Burney in 1894.[3] For more than a century since then, appendectomy has been the gold standard treatment for appendicitis and has been widely applied in clinical practice. However, the

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treatment of AA has been under active debate and discourse in recent years, and an increasing amount of evidence has shown that the majority of patients with uncomplicated acute appendicitis can be treated with antibiotics alone instead of surgery.[4-12] Therefore, the guidelines recommend antibiotic treatment for uncomplicated AA when patients accept the recurrence risk.[13]

At present, there is no consensus on the choice of antibiotics, and various antibiotic regimens have been adopted. Some recent clinical studies have focused on defining a better regimen, including the route of administration, course of treatment and even supportive care without antibiotics.[5, 14-19] A randomized clinical trial on antibiotic therapy for uncomplicated AA from Finland adopted antibiotic therapy with intravenous ertapenem for 3 days followed by 7 days of oral levofloxacin and metronidazole and showed that antibiotic therapy is noninferior to appendectomy. [15] Park et al. performed a single-blinded (participants only) trial and reported results regarding possible spontaneous resolution of uncomplicated acute appendicitis. [16] Recently, the APPAC group designed and published a protocol for a multicenter, double-blinded, placebo-controlled, superiority randomized study comparing antibiotic therapy with placebo for the treatment of CT scan-confirmed uncomplicated acute appendicitis, aiming to evaluate the role of antibiotics in the resolution of uncomplicated acute appendicitis (NCT03234296).

However, the antibiotics used in these trials are not the preferred choice in most countries, including China. According to our previous study, three generations of intravenously administered cephalosporins with or without nitroimidazoles are the most common regimens, and the usage of antimicrobial drug regimens in conservative treatment for AA lacks standardization and rationale.[20] Additionally, the usage of

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antibiotic regimens in clinical trials or guidelines also varies, which can cause confusion for physicians regarding the choice of conservative AA treatment.

The trial from Park et al. showed a higher tendency of recurrence of appendicitis in the no-antibiotic group than in the antibiotic group, although the authors did not detect significant differences, which may be because of the small sample size.[16] In addition, cephalosporins combined with nitroimidazoles as preoperative prophylactic antibiotic regimens have been proven to reduce the incidence of surgical site infection compared with cephalosporins alone in both noncomplicated and complicated AA patients.[21] A prospective double-blinded randomized controlled trial revealed a significant decrease in wound infection rates with 2 postoperative intravenous doses of antibiotics, suggesting that postoperative antibiotics are of benefit in simple appendicitis.[22] Some etiological studies also suggested that anaerobic bacteria in uncomplicated appendicitis are a nonnegligible risk factor for disease progression.[23, 24] Accordingly, we hypothesized that a combination of anti-anaerobe drug regimens would have stronger effects on decreasing the recurrence of AA.

To our knowledge, this double-blinded randomized controlled study is the first to evaluate the therapeutic efficiency (a composite primary outcome including in-hospital cure rate, transfer rate and recurrence rate within a one year follow-up period) of the anti-anaerobe covered strategy compared to anti-anaerobic uncovered regimens in uncomplicated AA, providing a reference for rational antibiotic selection.

Methods

Trial design

The OPTIMA trial is a multicenter, randomized, double-blinded, parallel controlled clinical trial designed to evaluate the therapeutic qualities and efficiency of a combination anti-anaerobe strategy compared with no use of anti-anaerobic agents.

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At each center, patients are randomly allocated to the experimental treatment arm (intravenously administered ceftazidime combined with ornidazole) or the control arm (intravenously administered ceftazidime combined with a saline simulation agent) in a 1:1 ratio. Figure 1 shows the enrollment process, interventions, and follow-up of participants in two conservative treatments for acute appendicitis.

Trial setting

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

Diagnosis

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

Inclusion criteria:

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1. Age 18-65 years

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

3. Diagnosis of uncomplicated AA confirmed by imaging (ultrasound, CT or MRI) defined by the following criteria: appendix diameter greater than 6 mm, thickened appendix wall, appendix lumen stenosis, inflammatory edema and a small amount of effusion around the appendix.

Exclusion criteria:

1. Age <18 or >65

2. AIR score>8

3. Diagnosis of existing complications by imaging (ultrasound, CT or MRI), such as abscess, appendiceal fecalith, or perforation

4. Appendiceal tumor and/or appendiceal soft tissue mass

5. History of acute or chronic appendicitis

6. Suspicion of severe sepsis

7. Patients with a known history of allergies or other contraindications to the study antibiotics

8. Immunocompromised patients

9. Patients undergoing other antibiotic treatments

10. Alcoholics

11. Women who are pregnant or plan to become pregnant or who are breastfeeding within 3 months of the study

12. Refusal to sign the informed consent

Allocation and randomisation

Due to differences in the volume of visits from each hospital, the data analyst will assign a fixed number of cases to each subcenter based on its annual volume of

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visits. SAS 9.1 software will be used to achieve stratified block randomization. The researchers will be blinded to the stratified randomization process and the results of patient randomization. At each center, after signing the informed consent, the patients meeting the trial criteria will be randomly assigned to arm A (ceftazidime combined with placebo group) or arm B (ceftazidime combined with ornidazole group) in a 1:1 ratio. Each patient will be given a unique study number, undergo random grouping and be assigned a designated treatment with 'Jinling Rat' random allocation software. The pharmacists will obtain treatment packages in similar containers that are distinguishable only by a patient's unique identification number. To ensure patient safety in an emergency, data analysts will provide each hospital with an emergency unblinding list that includes the specific drugs used by the patients participating in the trial. Each hospital should use it only in critical situations, such as when a patient has severe allergies to the treatment drug in the study.

Blinding

Jinling Rat software is a random allocation tool used to maintain double blinding throughout the whole process of the trial. The investigators and the patients remain unaware of the treatment packages until the study is finished and the data have been locked.

Follow-up will be conducted by the surgeon at each center either by telephone or outpatient visits. The surgeon who performs the follow-up is not aware of the patient's previous antibiotic regimen and records only the required information on the follow-up form.

Sample size calculation

Given the results of previous studies indicating that antibiotics have a success rate of approximately 75% in treating uncomplicated appendicitis, the recurrence rate

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within one year is 25-35%, and the recurrence rate with antibiotic treatment for appendicitis is highest within the three months after discharge,[7, 9, 15, 16] we estimate that the success rate of the combination of anti-anaerobic drugs can increase the cure rate from 75% to 80%. Under this condition, we calculated that a minimum of 1091 patients in each group would achieve a power of 0.8 (1-β) and a one-sided significance level (α) of 0.025 to conclude that the efficacy of the intervention arm is superior to that of the control arm regarding the long-term cure rate.

In addition, some relevant studies have chosen short-term efficacy as the primary outcome considering that AA is an acute phase disease and that antibiotics will not have effects on subjects after drug metabolism. Therefore, those studies have selected the response rate after a course of drug therapy as the primary outcome. Under this condition, we projected a sample size of 564 participants for each group with 90% power at a two-sided alpha level of 0.05 using PASS software (PASS 11, NCSS software, Kaysville, USA) to conclude that the efficacy of the intervention arm is superior to that of the control arm (from 96% to 99%).

Therefore, to sufficiently analyze both the short- and long-term efficacy of antibiotic therapy, we chose the first algorithm for sample size estimation, and a total of 2400 patients will be recruited, given an estimated dropout rate of 10% of all patients.

Recruitment plan

Recruitment of participants will start in January 2022 and follow-ups should be carried out at the same time. All 2400 patients are expected to be enrolled by the end of 2022.

Interventions

Antibiotic use protocol

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

Criteria for transferring to another treatment

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

Discharge and follow-up

Patients meeting the clinical cure criteria will be discharged, which means that the following criteria must be met at the same time: body temperature (underarm) <37.5℃, white blood cell count $<10.0\times10^9$/L, neutrophil percentage <70%, and no deep tenderness, mass or rebound pain in the right lower abdomen of the subjects during follow-up after treatment with the medication. According to the duration of

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conservative treatment, the hospitalization follow-up time will be set to 1 week. The following indicators will be collected on days 1, 3, 5, and 7: a physical examination, including the Visual Analog Scale (VAS), auxiliary examination, therapeutic effect, and surgery status (if any). An outpatient follow-up visit is recommended one week after discharge. Standard follow-ups of 2 weeks, 1 month, 3 months, 6 months, and 1 year will be performed by the surgeon either by telephone or in an outpatient setting. For patients treated surgically, follow-up should include the assessment of surgical site infection (SSI) in one month.

If the patient is treated conservatively or surgically for recurrent appendicitis after discharge, the time and components of treatment should be recorded.

Preparation before implementation

Before the commencement of the clinical trial, the investigators will be trained on the trial protocol by the head of each trial center. Each investigator should understand the content of this clinical trial protocol and master the standard methods of enrollment, recording, and judgment criteria according to Standard Operating Procedure (SOP) and Good Clinical Practice (GCP) guidelines. All participating surgeons and residents should accept standard training on the unified assessment methods for classifying different types of AA.

Outcome measures

Primary outcome measure

The primary endpoint of this study is evaluation of the efficiency and long-term outcome of ceftazidime combined with ornidazole compared with ceftazidime combined with placebo. It is hypothesized that ceftazidime combined with ornidazole is superior to ceftazidime combined with placebo and will increase the one-year cure rate. The efficiency of nonoperative management (NOM) of uncomplicated

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appendicitis will be measured on many aspects, including the initial cure rate, need for operation, and long-term recurrence rate.

The definition of recurrence is based on clinical, imaging, and/or histopathological diagnosis during follow-up. When subjects experience relevant symptoms and signs, further laboratory inspection and imaging diagnosis of acute appendicitis will be required. All patients with recurrent appendicitis will undergo a laparoscopic appendectomy. Histopathological diagnosis results and bacterial culture results during surgery will be recorded to identify recurrence.

Secondary outcome measures

Secondary endpoints are the evaluation of the total length of hospital stay, total expenses during hospitalization, mortality, duration of antibiotic treatment, complication rate, time to fulfill discharge criteria, pain score (VAS), the use of analgesics, quality of life assessment (SF-12), readmission rate, percentage of patients requiring appendectomy during initial antibiotic therapy, and the number of days absent from work. Complications will be classified according to conservative treatment, such as antibiotic-related adverse reactions, or surgery, such as the incidence of surgical site infection (SSI), incisional hernia, anastomotic fistula, abdominal abscess, and adhesions. The details of the data collection are shown in Figure 2.

Management and analysis of data

Data collection and management

The data managers of the statistical unit are responsible for the data management. At each subcenter, the complete raw information of patients will be stored in electronic medical records and paper medical records to facilitate later review. Baseline demographics, as well as the relevant variables of antibiotic

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treatment and surgery, will be recorded independently by two data administrators. All variables that need to be counted are provided in the full study protocol. These variables should be registered in case report forms (CRFs), which will be entered into ResMan, an electronic data collection and management system supported by the Chinese Clinical Trial Registry. Data will be encrypted and can be processed only with the authorization of the data managers. A detailed response questionnaire (DRQ) will be used by the data managers to record missing and incorrect data. Then, the investigator will verify the raw materials kept by the hospital.

Statistical analysis

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

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

2. PP set: This set includes all randomized subjects who complete all follow-ups as required by the protocol, have no major protocol violations, and have good compliance (medication compliance between 80%-120%).

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

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

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Categorical variables are described as the frequency and proportion. The one-sided 97.5% CI for proportion difference will be calculated to evaluate the treatment difference (one-sided test at α=0.025). The secondary outcomes will be analyzed using different statistical methods according to the types of data. The t test or Wilcoxon rank sum test is usually used to compare continuous variables between two groups, and the chi-square test or Fisher's exact probability test is usually used to compare categorical variables. P values less than 0.05 will be considered indicative of statistical significance for all secondary outcome analyses.

Safety and data monitoring

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

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

Ethics and dissemination

Ethics

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

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following the Helsinki Declaration and the relevant Chinese clinical trial research norms and regulations.

Patient and Public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research

Protection of the rights and interests of patients

Before the start of this trial, research physicians should inform patients of the trial details in writing, including the nature of the clinical trial, the purpose of the trial, the expected benefits and the risks. The researchers are responsible for protecting the privacy of the participating patients. Even if the patients decide to withdraw from the trial at any stage, their medical benefits and rights will not be affected in any way, and they can continue to receive other effective treatment. For possible adverse events, the experiment will also design corresponding solutions. In addition, after the experiment is completed, the patients will be given the results by telephone. Translated written consent is attached as a supplement file (Supplement Materials).

Dissemination plan

The trial findings will be published in peer-reviewed journals and will also be disseminated through presentations at national and/or international conferences.

Discussion

The optimization of nonoperative management of appendicitis, including the dosage form and duration of antibiotic use, is being actively researched.[15] However, the types of antibiotics used in studies vary, and the selected antibiotics are not common in many regions worldwide, such as low- and middle-level developing countries. In addition, the role of anti-anaerobic agents in the treatment of uncomplicated appendicitis remains to be explored and emphasized. These factors

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make it difficult for clinicians to choose a reasonable antibiotic regimen for the treatment of appendicitis.

According to our previous retrospective study, cephalosporin alone and cephalosporin combined with nitroimidazole are common clinical treatment protocols in China and have similar short-term outcomes in the treatment of uncomplicated AA. However, few studies have compared the long-term outcomes of the different treatment strategies due to the lack of follow-up information after discharge.[20] To our knowledge, to date, no double-blinded randomized controlled trials have compared three generations of cephalosporins combined with three generations of cephalosporins combined with ornidazole in the treatment of uncomplicated AA. Thus, we designed the OPTIMA trial to evaluate the safety and efficacy of a combination of anti-anaerobic agents in the treatment of uncomplicated AA and its prognostic impact. The results of this study are of great significance for guiding clinical antibiotic use in an environment where antibiotic treatment regimens are not standardized and rational.

Strengths and limitations of this study

In this trial, ultrasound, CT and MRI are both chosen as examination techniques for appendicitis, since the accurate distinction between complicated and uncomplicated AA is the key to rational treatment of appendicitis. Considering that CT is not available at night at several nonteaching hospitals, patients with milder conditions may be reluctant to undergo more expensive CT and MRI scans. If we exclude these patients, it might increase the selection bias of the trial due to economic and time factors. The overall sensitivity and specificity are 76% and 95% for ultrasound and 99% and 84% for CT, respectively, and MRI is at least as sensitive and specific as CT.[31-33] Moreover, recent studies have shown that the AIR score

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has an advantage in diagnosing appendicitis due to its high sensitivity and specificity.[25-30] Therefore, a combination of the AIR score and imaging will be used to diagnose uncomplicated appendicitis in this study. All examination items and results will be stored in a timely manner in the ResMan system, the data will be verified and re-evaluated at any time by the dedicated data management review committee (DMRC), and patients who do not meet the criteria for uncomplicated appendicitis will be excluded. Thus, the diagnosis of noncomplicated AA in this trial is ensured to be reliable.

In terms of antibiotic selection, ertapenem is a broad-spectrum antibiotic with an anti-anaerobic effect that has been shown to be effective in the treatment of appendicitis in previous studies and is recommended in the guidelines.[13] However, compared with ertapenem, which is expensive and difficult to obtain, the antibiotics chosen in this study are readily available and safe, which makes the optimized nonoperative treatment of appendicitis obtained from the experimental results easier to popularize. In addition, according to previous studies, antibiotic treatment for uncomplicated acute appendicitis was shown to have the highest recurrence rate during the first three months after discharge.[6, 7, 9] We speculate that this finding is related to anaerobic bacteria in the intestinal tract. Thus, we plan to test this by comparing ceftazidime plus placebo with ceftazidime plus ornidazole for uncomplicated AA because of the excellent anti-anaerobic activity of nitroimidazoles.

To date, this study has the largest sample size among uncomplicated AA studies to evaluate the short-term and long-term prognoses. This study not only discusses the efficacy of combined anti-anaerobic drugs in the treatment of uncomplicated appendicitis but also focuses on the cure rate and recurrence rate of patients during the

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follow-up period after discharge and explores methods for reducing the recurrence rate of appendicitis.

For uncomplicated AA, it is difficult to obtain bacteriological evidence from the patient's abdominal cavity. Therefore, the anti-anaerobic drugs were selected based on a 2016 study of clinical characteristics and antimicrobial patterns in complicated intra-abdominal infections in China.[34] In addition, a 2017 retrospective study of appendicitis treatment reached similar conclusions about antibiotic use.[20] Moreover, a sufficiently large sample and one year of standardized follow-up are required to investigate the effect of anti-anaerobic drugs on the long-term outcome of appendicitis. This is a challenge for the subcenters in how to conduct research operations in an emergency department setting and how to respond promptly and accurately to emergency problems.

Conclusion

The OPTIMA trial is a multicenter, double-blinded, placebo-controlled, superiority randomized study aiming to evaluate the role of anti-anaerobic bacterial antibiotics in the resolution of uncomplicated AA.

Declarations

Acknowledgements: We acknowledge Jingdong Junzhuo Pharmaceutical Co., LTD for providing the study drugs.

Authors' contributions: All authors were involved in the study design, and read and approved the final manuscript. J R, R S and P W contributed to conception and design of this study. J W and H J provided statistical advice. J W, H J, S L and X W are responsible for contacting with the subcenters. J R, R S, P W, X W and J W are members of data management review committee. J W and H J drafted the manuscript.

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Competing interests: Jingdong Junzhuo Pharmaceutical Co., LTD provides the study drugs (ornidazole and sodium chloride injection, ceftazidime injection and simulants) for this investigator-initiated study but has no influence on the study design, data analysis, or report. The investigators take full responsibility for the integrity and content of this paper. And the authors declare that they have no competing interests.

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Figure legends

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

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

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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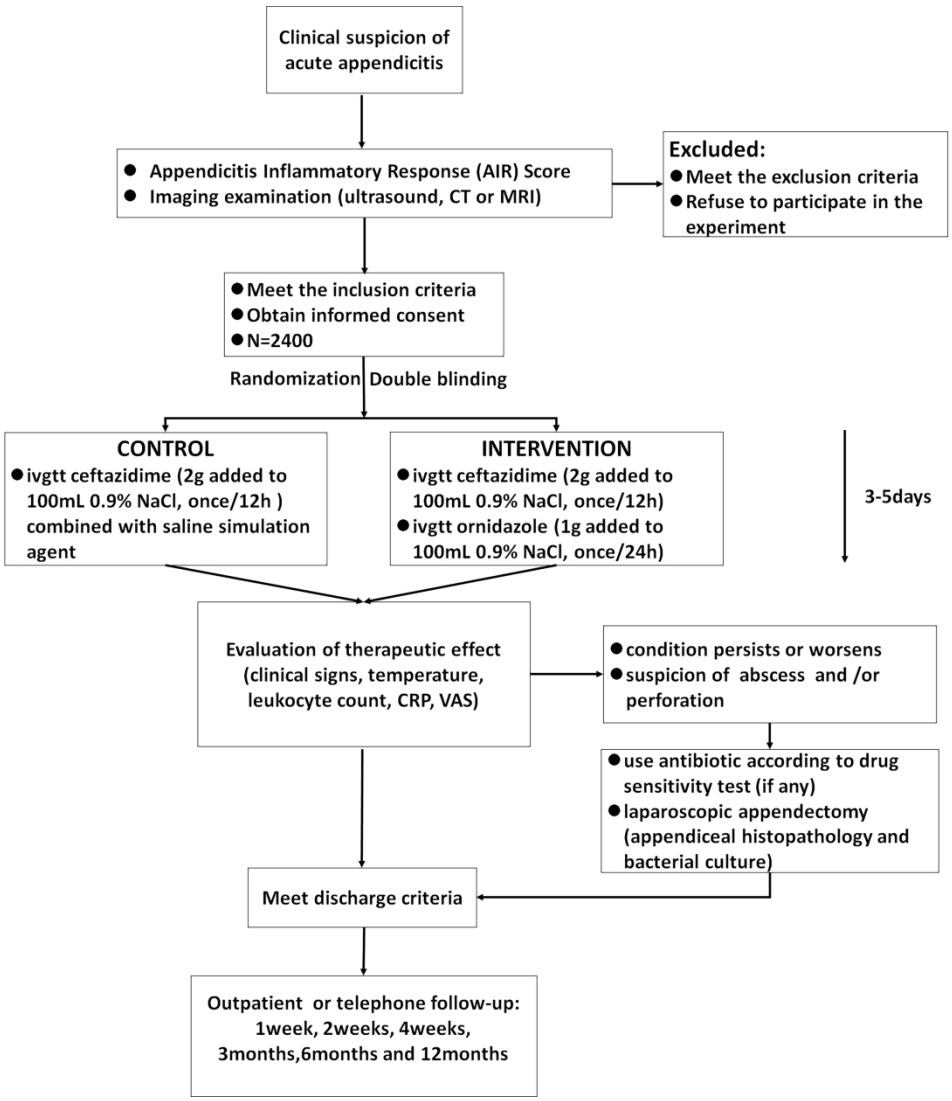

Figure 1: OPTIMA flowchart of enrollment, interventions, and follow-up. Abbreviation: ivgtt, intravenous drip; CRP, C reactive protein; VAS, Visual Analog Scale.

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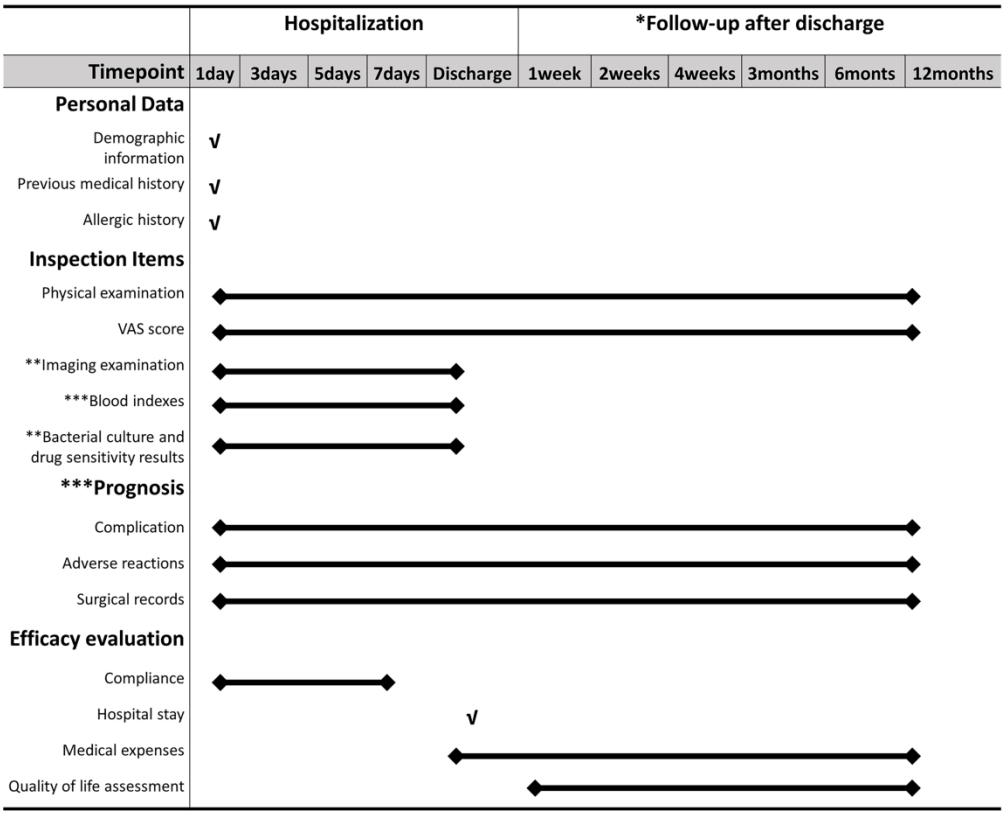

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CONSENT FORM

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.

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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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instead of additional examinations. If there is no need for further hospitalization, the follow-up after your treatment can be conducted by phone, outpatient service or WeChat, etc. Please confirm that you can cooperate with the doctor for follow-up within the specified follow-up time.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

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.

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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.

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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.

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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:

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SPIRIT
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
Administrative information			
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

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Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	P4/L70-133
	6b	Explanation for choice of comparators	P5/L101-113
Objectives	7	Specific objectives or hypotheses	P5/L114-118
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
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	P6/L130
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
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	P10/L224-234
	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
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	P11/L252-256
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	P10/L236-242
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
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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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
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	P10/L219-221
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	P7/L172-186
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
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	P8/L183
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
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	P14/L333-336
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	P13/L320-331
	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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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
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
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	P13/L308-319
	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
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	P14/L340-341
	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
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
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
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	P14/L346-349
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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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
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Detail in informed consent form
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
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	P18/L443-447
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
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
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	P15/L362-364
	31b	Authorship eligibility guidelines and any intended use of professional writers	Not applicable
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Not applicable
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	See supplement materials
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" license.

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

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

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Abstract

Introduction Emerging evidence has shown that an antibiotics-first strategy is a 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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Ethics and dissemination: The protocol has acquired the approve of the Ethics Committee of Jinling Hospital on November 13, 2018(2018NZKY-027-01). The trial findings will be published in peer-reviewed journals.

Trial registration: Chinese Clinical Trial Register, ChiCTR1800018896

Strengths and limitations of this study

Strength 1: The OPTIMA trial is the first multicenter, randomized, double-blinded, placebo-controlled clinical study comparing ceftazidime combined with ornidazole versus ceftazidime combined with placebo for uncomplicated acute appendicitis to investigate the role of anti-anaerobic drugs in the conservative treatment of appendicitis.

Strength 2: A double-blinded trial with a placebo can reduce bias and confirm the role of anti-anaerobic agents in the treatment of appendicitis.

Strength 3: The data will be collected and saved in an electronic data capture system (EDC) to guarantee the integrity of the data, and the data engineers will organize and check the data from each center to reduce errors in the data collection process.

Limitation 1: Since the treatment of uncomplicated appendicitis in this study involves antibiotics alone, we cannot collect data on surgical pathology and bacteriological analysis, unless surgical intervention is required.

Introduction

Acute appendicitis (AA) is one of the most common indications for emergency surgery worldwide.[1] In 2019, there were an estimated 17.7 million cases (incidence, 228/100,000).[2] Appendectomy was first proposed by Mc Burney in 1894.[3] For more than a century since then, appendectomy has been the gold standard treatment for appendicitis and has been widely applied in clinical practice. However, the

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treatment of AA has been under active debate and discourse in recent years, and an increasing amount of evidence has shown that the majority of patients with uncomplicated acute appendicitis can be treated with antibiotics alone instead of surgery.[4-12] Therefore, the guidelines recommend antibiotic treatment for uncomplicated AA when patients accept the recurrence risk.[13]

At present, there is no consensus on the choice of antibiotics, and various antibiotic regimens have been adopted. Some recent clinical studies have focused on defining a better regimen, including the route of administration, course of treatment and even supportive care without antibiotics.[5, 14-19] A randomized clinical trial on antibiotic therapy for uncomplicated AA from Finland adopted antibiotic therapy with intravenous ertapenem for 3 days followed by 7 days of oral levofloxacin and metronidazole and showed that antibiotic therapy is noninferior to appendectomy. [15] Park et al. performed a single-blinded (participants only) trial and reported results regarding possible spontaneous resolution of uncomplicated acute appendicitis. [16] Recently, the APPAC group designed and published a protocol for a multicenter, double-blinded, placebo-controlled, superiority randomized study comparing antibiotic therapy with placebo for the treatment of CT scan-confirmed uncomplicated acute appendicitis, aiming to evaluate the role of antibiotics in the resolution of uncomplicated acute appendicitis (NCT03234296).

However, the antibiotics used in these trials are not the preferred choice in most countries, including China. According to our previous study, three generations of intravenously administered cephalosporins with or without nitroimidazoles are the most common regimens, and the usage of antimicrobial drug regimens in conservative treatment for AA lacks standardization and rationale.[20] Additionally, the usage of

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antibiotic regimens in clinical trials or guidelines also varies, which can cause confusion for physicians regarding the choice of conservative AA treatment.

The trial from Park et al. showed a higher tendency of recurrence of appendicitis in the no-antibiotic group than in the antibiotic group. Considering Park's study was not a double-blind and multicenter study, it is necessary to conduct more larger sample size trials to prove the correctness of the conclusion.[16] In addition, cephalosporins combined with nitroimidazoles as preoperative prophylactic antibiotic regimens have been proven to reduce the incidence of surgical site infection compared with cephalosporins alone in both noncomplicated and complicated AA patients.[21] A prospective double-blinded randomized controlled trial revealed a significant decrease in wound infection rates with 2 postoperative intravenous doses of antibiotics, suggesting that postoperative antibiotics are of benefit in simple appendicitis.[22] Some etiological studies also suggested that anaerobic bacteria in uncomplicated appendicitis are a nonnegligible risk factor for disease progression.[23-26] Accordingly, we hypothesized that a combination of anti-anaerobe drug regimens would have stronger effects on decreasing the recurrence of AA.

To our knowledge, this double-blinded randomized controlled study is the first to evaluate the therapeutic efficiency (a composite primary outcome including in-hospital cure rate, transfer rate and recurrence rate within a one year follow-up period) of the anti-anaerobe covered strategy compared to anti-anaerobic uncovered regimens in uncomplicated AA, providing a reference for rational antibiotic selection.

Methods

Trial design

The OPTIMA trial is a multicenter, randomized, double-blinded, parallel controlled clinical trial designed to evaluate the therapeutic qualities and efficiency of

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a combination anti-anaerobe strategy compared with no use of anti-anaerobic agents. At each center, patients are randomly allocated to the experimental treatment arm (intravenously administered ceftazidime combined with ornidazole) or the control arm (intravenously administered ceftazidime combined with a saline simulation agent) in a 1:1 ratio. Figure 1 shows the enrollment process, interventions, and follow-up of participants in two conservative treatments for acute appendicitis.

Trial setting

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

Diagnosis

A rapid and correct diagnosis of uncomplicated appendicitis is the key to the success of the study. First, imaging has irreplaceable advantages in the diagnosis and differentiation of uncomplicated appendicitis. Moreover, due to the high sensitivity and specificity of the appendicitis inflammatory response (AIR) score in the identification of advanced appendicitis, we combined the AIR score and imaging tests to diagnose uncomplicated appendicitis.[27-32] All patients with clinically suspected AA will be enrolled for further screening. Clinical history, physical examination and laboratory tests, including routine blood tests (white cell count, proportion of polymorphonuclear leukocytes), C-reactive protein (CRP), creatinine, and female human chorionic gonadotropin (HCG), will be evaluated by the surgeon. The AIR score will be recorded according to the inspection results to define three groups: low probability (<5 points), medium probability (5–8 points), and high probability (>8 points). Then, all patients will undergo imaging.

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Inclusion criteria:

1. Age 18-65 years

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

3. Diagnosis of uncomplicated AA confirmed by imaging (ultrasound, CT or MRI) defined by the following criteria: appendix diameter greater than 6 mm, thickened appendix wall, appendix lumen stenosis, inflammatory edema and a small amount of effusion around the appendix.

Exclusion criteria:

1. Age <18 or >65

2. AIR score>8

3. Diagnosis of existing complications by imaging (ultrasound, CT or MRI), such as abscess, appendiceal fecalith, or perforation

4. Appendiceal tumor and/or appendiceal soft tissue mass

5. History of acute or chronic appendicitis

6. Suspicion of severe sepsis

7. Patients with a known history of allergies or other contraindications to the study antibiotics

8. Immunocompromised patients

9. Patients undergoing other antibiotic treatments

10. Alcoholics

11. Women who are pregnant or plan to become pregnant or who are breastfeeding within 3 months of the study

12. Refusal to sign the informed consent

Allocation and randomisation

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Due to differences in the volume of visits from each hospital, the data analyst will assign a fixed number of cases to each subcenter based on its annual volume of visits. SAS 9.1 software will be used to achieve stratified block randomization. The researchers will be blinded to the stratified randomization process and the results of patient randomization. At each center, after signing the informed consent, the patients meeting the trial criteria will be randomly assigned to arm A (ceftazidime combined with placebo group) or arm B (ceftazidime combined with ornidazole group) in a 1:1 ratio. Each patient will be given a unique study number, undergo random grouping and be assigned a designated treatment with 'Jinling Rat' random allocation software. The pharmacists will obtain treatment packages in similar containers that are distinguishable only by a patient's unique identification number. To ensure patient safety in an emergency, data analysts will provide each hospital with an emergency unblinding list that includes the specific drugs used by the patients participating in the trial. Each hospital should use it only in critical situations, such as when a patient has severe allergies to the treatment drug in the study.

Blinding

Jinling Rat software is a random allocation tool used to maintain double blinding throughout the whole process of the trial. The investigators and the patients remain unaware of the treatment packages until the study is finished and the data have been locked.

Follow-up will be conducted by the surgeon at each center either by telephone or outpatient visits. The surgeon who performs the follow-up is not aware of the patient's previous antibiotic regimen and records only the required information on the follow-up form.

Sample size calculation

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Given the results of previous studies indicating that antibiotics have a success rate of approximately 75% in treating uncomplicated appendicitis, the recurrence rate within one year is 25-35%, and the recurrence rate with antibiotic treatment for appendicitis is highest within the three months after discharge,[7, 9, 15, 16] we estimate that the success rate of the combination of anti-anaerobic drugs can increase the cure rate from 75% to 80%. Under this condition, we calculated that a minimum of 1091 patients in each group would achieve a power of 0.8 (1-β) and a one-sided significance level (α) of 0.025 to conclude that the efficacy of the intervention arm is superior to that of the control arm regarding the long-term cure rate.

In addition, some relevant studies have chosen short-term efficacy as the primary outcome considering that AA is an acute phase disease and that antibiotics will not have effects on subjects after drug metabolism. Therefore, those studies have selected the response rate after a course of drug therapy as the primary outcome. Under this condition, we projected a sample size of 564 participants for each group with 90% power at a two-sided alpha level of 0.05 using PASS software (PASS 11, NCSS software, Kaysville, USA) to conclude that the efficacy of the intervention arm is superior to that of the control arm (from 96% to 99%).

Therefore, to sufficiently analyze both the short- and long-term efficacy of antibiotic therapy, we chose the first algorithm for sample size estimation, and a total of 2400 patients will be recruited, given an estimated dropout rate of 10% of all patients.

Recruitment plan

Recruitment of participants will start in January 2022 and follow-ups should be carried out at the same time. All 2400 patients are expected to be enrolled by the end of 2022.

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Interventions

Antibiotic use protocol

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

Criteria for transferring to another treatment

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

Discharge and follow-up

Patients meeting the clinical cure criteria will be discharged, which means that the following criteria must be met at the same time: body temperature (underarm) <37.5℃, white blood cell count $<10.0\times10^9$/L, neutrophil percentage <70%, and no

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deep tenderness, mass or rebound pain in the right lower abdomen of the subjects during follow-up after treatment with the medication. According to the duration of conservative treatment, the hospitalization follow-up time will be set to 1 week. The following indicators will be collected on days 1, 3, 5, and 7: a physical examination, including the Visual Analog Scale (VAS), auxiliary examination, therapeutic effect, and surgery status (if any). An outpatient follow-up visit is recommended one week after discharge. Standard follow-ups of 2 weeks, 1 month, 3 months, 6 months, and 1 year will be performed by the surgeon either by telephone or in an outpatient setting. For patients treated surgically, follow-up should include the assessment of surgical site infection (SSI) in one month.

If the patient is treated conservatively or surgically for recurrent appendicitis after discharge, the time and components of treatment should be recorded.

Preparation before implementation

Before the commencement of the clinical trial, the investigators will be trained on the trial protocol by the head of each trial center. Each investigator should understand the content of this clinical trial protocol and master the standard methods of enrollment, recording, and judgment criteria according to Standard Operating Procedure (SOP) and Good Clinical Practice (GCP) guidelines. All participating surgeons and residents should accept standard training on the unified assessment methods for classifying different types of AA.

Outcome measures

Primary outcome measure

The primary endpoint of this study is evaluation of the efficiency and long-term outcome of ceftazidime combined with ornidazole compared with ceftazidime combined with placebo. It is hypothesized that ceftazidime combined with ornidazole

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is superior to ceftazidime combined with placebo and will increase the one-year cure rate. The efficiency of nonoperative management (NOM) of uncomplicated appendicitis will be measured on many aspects, including the initial cure rate, need for operation, and long-term recurrence rate.

The definition of recurrence is based on clinical, imaging, and/or histopathological diagnosis during follow-up. When subjects experience relevant symptoms and signs, further laboratory inspection and imaging diagnosis of acute appendicitis will be required. All patients with recurrent appendicitis will undergo a laparoscopic appendectomy. Histopathological diagnosis results and bacterial culture results during surgery will be recorded to identify recurrence.

Secondary outcome measures

Secondary endpoints are the evaluation of the total length of hospital stay, total expenses during hospitalization, mortality, duration of antibiotic treatment, complication rate, time to fulfill discharge criteria, pain score (VAS), the use of analgesics, quality of life assessment (SF-12), readmission rate, percentage of patients requiring appendectomy during initial antibiotic therapy, and the number of days absent from work. Complications will be classified according to conservative treatment, such as antibiotic-related adverse reactions, or surgery, such as the incidence of surgical site infection (SSI), incisional hernia, anastomotic fistula, abdominal abscess, and adhesions. The details of the data collection are shown in Figure 2.

Management and analysis of data

Data collection and management

The data managers of the statistical unit are responsible for the data management. At each subcenter, the complete raw information of patients will be

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stored in electronic medical records and paper medical records to facilitate later review. Baseline demographics, as well as the relevant variables of antibiotic treatment and surgery, will be recorded independently by two data administrators. All variables that need to be counted are provided in the full study protocol. These variables should be registered in case report forms (CRFs), which will be entered into ResMan, an electronic data collection and management system supported by the Chinese Clinical Trial Registry. Data will be encrypted and can be processed only with the authorization of the data managers. A detailed response questionnaire (DRQ) will be used by the data managers to record missing and incorrect data. Then, the investigator will verify the raw materials kept by the hospital.

Statistical analysis

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

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

2. PP set: This set includes all randomized subjects who complete all follow-ups as required by the protocol, have no major protocol violations, and have good compliance (medication compliance between 80%-120%).

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

All statistical analyses will be performed with SAS 9.1 system programming. All statistical tests, except for the superiority test (a one-sided test) of the primary

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measures, will be conducted on a bilateral basis. Continuous variables are described as the mean and standard deviation or median and upper and lower quartiles. Categorical variables are described as the frequency and proportion. The one-sided 97.5% CI for proportion difference will be calculated to evaluate the treatment difference (one-sided test at α=0.025). The secondary outcomes will be analyzed using different statistical methods according to the types of data. The t test or Wilcoxon rank sum test is usually used to compare continuous variables between two groups, and the chi-square test or Fisher's exact probability test is usually used to compare categorical variables. P values less than 0.05 will be considered indicative of statistical significance for all secondary outcome analyses.

Safety and data monitoring

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

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

Ethics and dissemination

Ethics

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The protocol has acquired the approval of the Ethics Committee of Jinling Hospital on November 13, 2018(2018NZKY-027-01). This trial will be conducted following the Helsinki Declaration and the relevant Chinese clinical trial research norms and regulations.

Patient and Public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research

Protection of the rights and interests of patients

Before the start of this trial, research physicians should inform patients of the trial details in writing, including the nature of the clinical trial, the purpose of the trial, the expected benefits and the risks. The researchers are responsible for protecting the privacy of the participating patients. Even if the patients decide to withdraw from the trial at any stage, their medical benefits and rights will not be affected in any way, and they can continue to receive other effective treatment. For possible adverse events, the experiment will also design corresponding solutions. In addition, after the experiment is completed, the patients will be given the results by telephone. Translated written consent is attached as a supplement file (Supplement Materials).

Dissemination plan

The trial findings will be published in peer-reviewed journals and will also be disseminated through presentations at national and/or international conferences.

Discussion

The optimization of nonoperative management of appendicitis, including the dosage form and duration of antibiotic use, is being actively researched.[15] However, the types of antibiotics used in studies vary, and the selected antibiotics are not common in many regions worldwide, such as low- and middle-level developing

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countries. In addition, the role of anti-anaerobic agents in the treatment of uncomplicated appendicitis remains to be explored and emphasized. These factors make it difficult for clinicians to choose a reasonable antibiotic regimen for the treatment of appendicitis.

Some studies showed that only supportive care of uncomplicate AA or diverticulitis is noninferior to antibiotics.[16, 33, 34] However, a number of etiological studies have demonstrated that anaerobic bacteria especially Fusobacterium nucleatum/necrophorum are a nonnegligible risk factor for acute appendicitis. [23-26] There is currently a lack of a multicenter randomized controlled trial exploring the necessity of anti-anaerobic agents in the NOM of uncomplicated appendicitis.

According to our previous retrospective study, cephalosporin alone and cephalosporin combined with nitroimidazole are common clinical treatment protocols in China and have similar short-term outcomes in the treatment of uncomplicated AA. However, few studies have compared the long-term outcomes of the different treatment strategies due to the lack of follow-up information after discharge.[20] To our knowledge, to date, no double-blinded randomized controlled trials have compared three generations of cephalosporins combined with three generations of cephalosporins combined with ornidazole in the treatment of uncomplicated AA. Thus, we designed the OPTIMA trial to evaluate the safety and efficacy of a combination of anti-anaerobic agents in the treatment of uncomplicated AA and its prognostic impact. The results of this study are of great significance for guiding clinical antibiotic use in an environment where antibiotic treatment regimens are not standardized and rational.

Strengths and limitations of this study

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In this trial, ultrasound, CT and MRI are both chosen as examination techniques for appendicitis, since the accurate distinction between complicated and uncomplicated AA is the key to rational treatment of appendicitis. Considering that CT is not available at night at several nonteaching hospitals, patients with milder conditions may be reluctant to undergo more expensive CT and MRI scans. If we exclude these patients, it might increase the selection bias of the trial due to economic and time factors. The overall sensitivity and specificity are 76% and 95% for ultrasound and 99% and 84% for CT, respectively, and MRI is at least as sensitive and specific as CT.[35-37] Moreover, recent studies have shown that the AIR score has an advantage in diagnosing appendicitis due to its high sensitivity and specificity.[27-32] Therefore, a combination of the AIR score and imaging will be used to diagnose uncomplicated appendicitis in this study. All examination items and results will be stored in a timely manner in the ResMan system, the data will be verified and re-evaluated at any time by the dedicated data management review committee (DMRC), and patients who do not meet the criteria for uncomplicated appendicitis will be excluded. Thus, the diagnosis of noncomplicated AA in this trial is ensured to be reliable.

In terms of antibiotic selection, ertapenem is a broad-spectrum antibiotic with an anti-anaerobic effect that has been shown to be effective in the treatment of appendicitis in previous studies and is recommended in the guidelines.[13] However, compared with ertapenem, which is expensive and difficult to obtain, the antibiotics chosen in this study are readily available and safe, which makes the optimized nonoperative treatment of appendicitis obtained from the experimental results easier to popularize. In addition, according to previous studies, antibiotic treatment for uncomplicated acute appendicitis was shown to have the highest recurrence rate

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during the first three months after discharge.[6, 7, 9] We speculate that this finding is related to anaerobic bacteria in the intestinal tract. Thus, we plan to test this by comparing ceftazidime plus placebo with ceftazidime plus ornidazole for uncomplicated AA because of the excellent anti-anaerobic activity of nitroimidazoles.[38-40]

To date, this study has the largest sample size among uncomplicated AA studies to evaluate the short-term and long-term prognoses. This study not only discusses the efficacy of combined anti-anaerobic drugs in the treatment of uncomplicated appendicitis but also focuses on the cure rate and recurrence rate of patients during the follow-up period after discharge and explores methods for reducing the recurrence rate of appendicitis.

For uncomplicated AA, it is difficult to obtain bacteriological evidence from the patient's abdominal cavity. In this study, bacteriological information about AA was collected only at the time of surgical treatment. Therefore, the anti-anaerobic drugs were selected based on a 2016 study of clinical characteristics and antimicrobial patterns in complicated intra-abdominal infections in China.[41] In addition, a 2017 retrospective study of appendicitis treatment reached similar conclusions about antibiotic use.[20] There were other limitations to this study. We did not set a placebo group with only supportive care considering the safety and interests of patients. Even though, it is feasible to explore the role of anti-anaerobic agents in uncomplicated appendicitis. Moreover, a sufficiently large sample and one year of standardized follow-up are required to investigate the effect of anti-anaerobic drugs on the long-term outcome of appendicitis. This is a challenge for the subcenters in how to conduct research operations in an emergency department setting and how to respond promptly and accurately to emergency problems.

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Declarations

Acknowledgements: We acknowledge Jingdong Junzhuo Pharmaceutical Co., LTD for providing the study drugs.

Authors' contributions: All authors were involved in the study design, and read and approved the final manuscript. J R, R S and P W contributed to conception and design of this study. J W and H J provided statistical advice. J W, H J, S L and X W are responsible for contacting with the subcenters. J R, R S, P W, X W and J W are members of data management review committee. J W and H J drafted the manuscript.

Competing interests: Jingdong Junzhuo Pharmaceutical Co., LTD provides the study drugs (ornidazole and sodium chloride injection, ceftazidime injection and simulants) for this investigator-initiated study but has no influence on the study design, data analysis, or report. The investigators take full responsibility for the integrity and content of this paper. And the authors declare that they have no competing interests.

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Figure legends

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

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

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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** 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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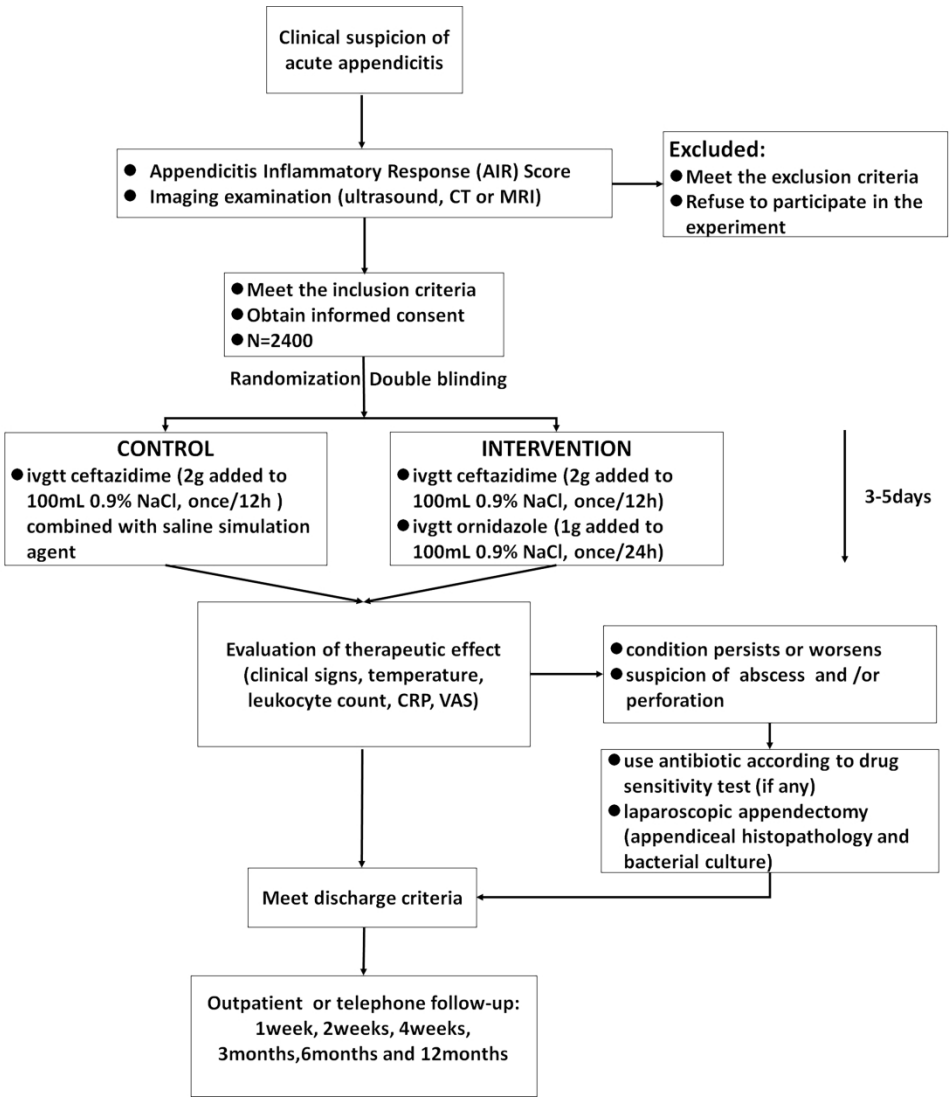

Figure 1: OPTIMA flowchart of enrollment, interventions, and follow-up. Abbreviation: ivgtt, intravenous drip; CRP, C reactive protein; VAS, Visual Analog Scale.

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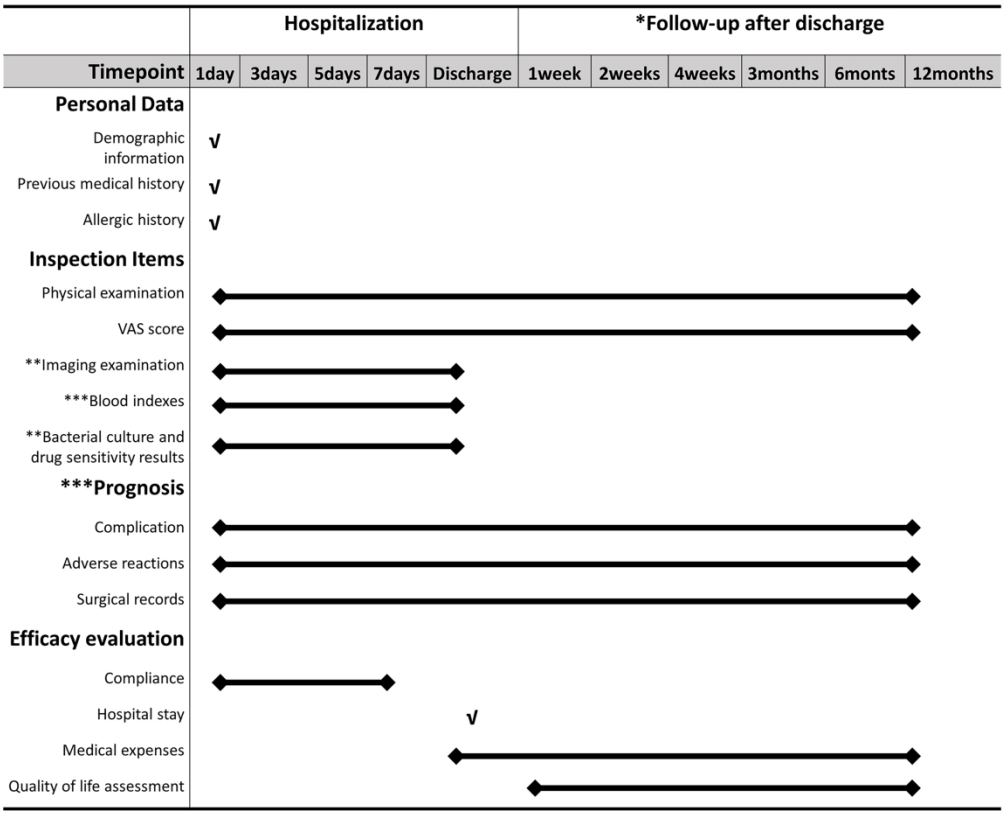

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CONSENT FORM

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.

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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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instead of additional examinations. If there is no need for further hospitalization, the follow-up after your treatment can be conducted by phone, outpatient service or WeChat, etc. Please confirm that you can cooperate with the doctor for follow-up within the specified follow-up time.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

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.

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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.

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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.

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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:

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
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

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Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	P4/L70-133
	6b	Explanation for choice of comparators	P9/L219-221
Objectives	7	Specific objectives or hypotheses	P5/L112-113
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
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	P6/L130
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
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	P10/L222-242
	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
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	P11/L252-256
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	P10/L236-242
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
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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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
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	P10/L219-221
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	P7/L172-186
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
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	P8/L183
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
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	P14/L333-336
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	P13/L320-331
	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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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
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
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	P13/L308-319
	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
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	P14/L340-341
	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
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
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
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	P14/L346-349
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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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
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Detail in informed consent form
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
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	P18/L455-459
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
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
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	P15/L364-365
	31b	Authorship eligibility guidelines and any intended use of professional writers	Not applicable
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Not applicable
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	See supplement materials
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" license.

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