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Protocol for Extended Antibiotic Therapy after Laparoscopic Cholecystectomy for Acute Calculus Cholecystitis. Is it Necessary?

(Cholecystectomy Antibiotic Randomized Trial - CHART)

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Abstract

Introduction: Acute calculus cholecystitis represents one of the most common complications of cholelithiasis. While laparoscopic cholecystectomy is the standard treatment in mild and moderate forms, the need of antibiotic therapy after surgery remains undefined. The aim of the randomized controlled CHART trial is therefore to assess if there are benefits in the use of postoperative antibiotics in patients with mild or moderate acute cholecystitis in whom a laparoscopic cholecystectomy is performed.

Methods and analysis: Single-centre, double-blind, randomized trial. After screening for eligibility and informed consent, 300 patients admitted for acute calculus cholecystitis will be randomized into 2 groups of treatment, either receiving amoxicillin/clavulanic acid or placebo for 5 consecutive days. Post-operative evaluation will take place during the first 30 days. Post-operative infectious complications are the primary endpoint. Secondary endpoints are length of hospital stay, readmissions, need of re-intervention (percutaneous or surgical re-interventions) and overall mortality. The results of this trial will provide strong evidence to either support or abandon the use of antibiotics after surgery, impacting directly in the incidence of adverse events associated to the use of antibiotics, the emergence of bacterial resistance and treatment costs.

Ethics and dissemination: This study and informed consent sheets have been approved by the Research Projects Evaluating Committee (CEPI) of HIBA (protocol Nº 2111). Results of the trial will be reported in a peer-reviewed publication.

Trial registration: This study is registered at Clinicaltrial.gov database (ClinicalTrials.gov Identifier: NCT02057679).

Introduction

More than 90% of the cases of acute calculus cholecystitis (ACC) are associated with gallstones[1 2]. ACC represents one of the most common complications of cholelithiasis, which can be found in 20% of symptomatic patients. It is known that the initial event in ACC is the obstruction of the gallbladder's drainage due to an impacted gallstone in the Hartmann's pouch or the cystic duct. Intraluminal pressure increases, reducing blood irrigation and lymphatic drainage, which finally produces gallbladder inflammation. It is assumed that this inflammation is initially sterile. However, if the obstruction persists, infection can develop, commonly with bacteria of the family of Enterobacteriacea, *Enteroccocus spp* and anaerobes[2-4].

The diagnostic criteria and severity assessment of acute cholecystitis have been well established in the 2007 Tokyo Guidelines, updated in 2013. According to these guidelines, ACC is classified as mild (Grade I), moderate (Grade II) and severe (Grade III). Severe acute cholecystitis is associated with at least one organ dysfunction. Moderate acute cholecystitis is associated with any of the following conditions: elevated WBC count (18,000/mm3); palpable tender mass in the right upper abdominal quadrant; duration of complaints for more than 72 hours; marked local inflammation (gangrenous cholecystitis, pericholecystic abscess, hepatic abscess, biliary peritonitis, emphysematous cholecystitis). Mild acute cholecystitis does not meet the criteria of any of the formers. It can also be defined as an acute cholecystitis in a healthy patient with no organ dysfunction with only mild inflammatory changes in the gallbladder[5].

While laparoscopic cholecystectomy (LC) is the gold standard treatment of mild and moderate forms of ACC, the need for antibiotic therapy after surgery continues to be a matter of debate. There is a lack of evidence regarding duration and type of

antimicrobial therapy after surgery[2 6]. The updated Tokyo Guidelines propose to administer antibiotics only up to 24 hours after surgery for mild ACC and 4-7 days in moderate or severe cases[4]. It has been suggested that a beta-lactam monoscheme (i.e. amoxicillin/clavulanic acid [AMC]) would be adequate in patients with mild and moderate cholecystitis without intraoperative complications such as bile peritonitis, cholangitis, gallbladder perforation or abscesses[4 7]. However, the real benefits of its use in these situations have not been well studied.

Adverse effects of antibiotics are well known, such as allergic reactions and development of antibiotic resistance of bacterial species. The frequency of toxicodermia is 7-8% with the use amoxicillin, allergy reactions are accounted for in 1% of the patients, and the incidence of anaphylactic shock is 0,01-0,04% with the use of penicillin. Therefore, efforts are made to minimize the use of antibiotics in various fields in clinical medicine[8]. Hence, we decided to conduct a RCT in patients undergoing LC for mild and moderate ACC, randomizing patients to receive AMC or placebo after surgery. The primary objective of the present trial is to assess whether antibiotic treatment after LC in mild or moderate ACC reduces the incidence of postoperative infectious complications. The hypothesis is that postoperative antibiotics have no positive impact in patient's outcome and, therefore, should not be indicated in this subset of patients.

Methods and analysis

Trial design and randomization

The CHART trial is a randomized, controlled and blind to patient, investigator and data analysts study, which compares antibiotic treatment after LC due to mild and moderate ACC versus no antibiotic treatment. After screening for eligibility and informed consent

is obtained, patients will be randomized in a 1:1 ratio into one of the following study groups after LC:

• Antibiotic treatment

• Placebo

Patients will be randomized using the online randomizer provided by the Hospital Italiano Statistics Department (http://protocolos.hospitalitaliano.org.ar). Treatment according to randomization (Figure 1) must be carried out within 72 hours after randomization. Neither the researchers nor the patients will have knowledge of the assigned treatment until the end of the study. Each Treatment Pack (TP) will have a code to retrospectively help identify which group of treatment the patient was assigned to. Each TP contain tablets for a 5-day-treatment to be administered 3 times per day. The tablets will be provided by the Hospital Italiano de Buenos Aires (HIBA) Central Pharmacy.

Trial organization

Trial population and patient recruitment

All consecutive patients with the new diagnosis of mild or moderate ACC according to the Revised Tokyo Guidelines[5] admitted to the HIBA will be screened for eligibility to be enrolled in the CHART trial.

Patients will be approached for randomized inclusion if they meet each of the following inclusion criteria: diagnosis of mild or moderate ACC; willingness to participate in the study; ability to understand the nature of the study and what will be required of them; men or non-pregnant, non-lactating woman between 18 and 85 years of age who undergo early LC (before 3 days after the onset of the symptoms).

Exclusion criteria are: rejection to participate in the trial or the process of informed consent; hypersensitivity to AMC or lactose (used in placebo); severe ACC; moderate ACC associated with liver and/or gallbladder abscesses, cholangitis or bile peritonitis; intraoperative findings such as liver cancer, liver metastases, common bile duct stones or gallbladder carcinoma; conversion to laparotomy; previous treatment with antibiotics for more than 5 days; active oncological diseases; acquired immunodeficiency syndrome (AIDS); transplanted patients.

Trial interventions

All patients admitted to HIBA from January 2014 with mild or moderate AAC were invited to participate in the study. During the preoperative period, patients are randomly assigned to either group of intervention. Patients in both groups will receive parenteral hydration, gastric protection with protons pump inhibitors, analgesics and treatment with AMC intravenously every 8 hours until surgery, which has to be performed within 3 days after admission. No extra dose of AMC will be administered during surgery.

After the procedure treatment will be as follows:

***Experimental group*: Antibiotic treatment after surgery**

Patients in the experimental group will receive 1000 mg of AMC orally every 8 hours for 5 days, immediately after the surgery.

***Control group*: Placebo treatment after surgery**

Patients in the control group will receive placebo orally every 8 hours for 5 days, immediately after the surgery.

Study objectives and endpoints

The primary objective of the present trial is to assess whether antibiotic treatment after LC in mild or moderate ACC reduces the incidence of postoperative infectious complications.

Primary endpoint

The primary efficacy endpoint is postoperative infectious complications, defined as any infection occurring within the first 30 postoperative days, classified according to Clavien-Dindo Classification[9]. After randomization patients will be followed-up for 30 days.

Secondary endpoints

- Length of hospital stay: number of days from admission to hospital discharge.
- Readmission: need of readmission due to postoperative complications that require hospital care (hydration, intravenous antibiotics, percutaneous drainage, surgical treatment).
- Reintervention: need of surgical treatment under general anesthesia or percutaneous procedure in complicated patients.
- Overall mortality: deaths occurred in the first postoperative month.

Trial implementation

Inclusion, evaluation and follow-up

Patients will be screened according to the eligibility criteria and asked for written informed consent. Afterwards, they will be allocated randomly to each of both study groups.

Study schedule

The evaluation schedule for all patients will be as follows:

Stage 1= Every patient included in the protocol will be registered in a sheet containing personal information and data on the primary and secondary endpoints.

TP will be administered during the five postoperative days. On days 7 and 30, patients will be monitored in the outpatient's office. Patients will be given contact telephone numbers in case they have any concern or need to report any event during follow-up. All data collected will be registered in the follow-up sheet.

Stage 2= During this stage, researchers will carry out a statistical analysis of the analyzed variables and their relations.

Sample size

We hypothesized that the absence of postoperative antibiotic treatment would not be inferior to receiving antibiotics after surgery for the development of surgical site and distant infections after cholecystectomy. Our sample size calculation was based on published data[10-13] and on an expected postoperative infection rate in the antibiotic group of 3%. Assuming a non-inferiority margin of 5%, a one-tailed alpha error of 5% and a power of 80% to reject this null hypothesis, we estimated that the required sample size would be 150 cases in each group.

Statistical analysis

Confirmatory analysis

A non-inferiority design was chosen. The results were analyzed on an intention-to-treat basis. The association between outcome and the assigned treatment will be evaluated using the CHI^2 TEST in discrete variables and ANOVA for continuous variables. All data analysis will be performed using the SPSS® software package version 17.0 (SPSS, Chicago, Illinois, USA).

Clinical management and abandonment

Each patient is informed to be free to abandon the treatment at any time by informing the researchers. If the medical team or researchers consider that the patient is at risk due to the study, the patient will be removed and the doctors will provide feedback to the patient.

Damage and complications

If the patient presents any infectious complication during the postoperative stage or any sign of persistent infection such as leukocytosis, fever over 38ºC (100.4ºF), hepatogram alterations, cholangitis or hepatic abscesses, the medical team will proceed to stop the administration of TP and decide which medical actions need to be taken according to each particular case. Any adverse event detected during outpatient monitoring will be registered and classified according to its severity into mild, moderate and severe:

1- Mild: transitory events that do not require special treatment. These events do not affect patient's daily life.
2- Moderate: events that interfere in the patient's daily routine that require minimal, local or noninvasive intervention.
3- Severe: medically significant, disabling or immediately life-threatening events that require hospitalization and/or urgent intervention.

Ethics and dissemination

Ethics approval

The CHART trial is conducted in line with the current national and international regulations: World Medical Association Declaration of Helsinki, Regulation 5330/07

ANMAT, the Standards of Good Practices ICH E6 and the laws and regulations of the country, providing the greatest protection of the patient. The trial protocol and informed consent sheets have been approved by the Research Projects Evaluating Committee (CEPI) of HIBA (protocol Nº 2111). The CHART trial has been registered at Clinicaltrial.gov database (**ClinicalTrials.gov, Identifier:** NCT02057679).

Informed consent and confidentiality

In all cases, the participation in the study is voluntary and certified by the process of informed consent. The right to refuse to participate in the study will be respected at all times without any implications in the treatment of the patient disease. The antibiotics proposed correspond to the empirical initial scheme that is in use in our institution for patients with inflammatory/infectious hepato-biliary affections acquired in the community. All data collected will be treated with confidentiality and anonymously. Authorized personnel can only access the records of the study in compliance with the current legal regulation: National Law of Personal Information Protection No. 25.326 (Habeas Data Law).

All patients will be informed of the aims of the study, the possible adverse events, the procedures and possible hazards to which he/she will be exposed, and the mechanism of treatment allocation. Furthermore, it is the responsibility of the investigator to explain the patients their duties within the trial. They will be informed about the strict confidentiality of their personal data, but that their medical records may be reviewed for trial purposes by authorized individuals other than their treating physician. Trial findings will be stored in accordance with local data protection law/ICH GCP-Guidelines and will be handled in the strictest confidence. For protection of these data,

organizational procedures are implemented to prevent distribution of data to unauthorized people.

Dissemination

Anonymised results of the study will be published in a peer-reviewed journal, and will be presented at academic meetings and scientific conferences. Only the registered investigators will have access to the individual patient data.

Discussion

Although ACC is one of the most common diseases in general surgery, few trials have assessed the role of antibiotic therapy after LC. Most publications on the subject analyze the use of antibiotics after conventional procedures, or mix in the same design open and laparoscopic procedures.

In the late 1980s, Lau et al randomized 203 patients and compared a short course of 2 doses versus a long course of 7 days of cefamandole after early open cholecystectomy. They found that the short course was as effective as the long one in reducing postoperative infectious complications with the additional advantages of lower costs, risks of adverse events and length of hospital stay[14]. This was the first study to suggest that a reduction in the use of postoperative antibiotics may be possible. However, this study is outdated given the many changes in bacterial resistance over time and the modern surgical therapies. In addition to these findings, Mazeh et al conducted a randomized controlled trial (RCT) in which they demonstrated that the addition of intravenous antibiotic treatment to supportive care has limited, if any, effect in patients with mild ACC[3].

Recently, Regimbeau et al. published a multicenter RCT in which patients admitted with mild and moderate ACC were randomized to antibiotics or no treatment after surgery[15]. To the author's opinion, the main limitation of this study is that it includes both conventional and laparoscopic approaches (15% open cholecystectomies and a 10% conversion rate). It has been widely demonstrated that one of the advantages of laparoscopic approach is that it is associated with less surgical side infections rate[16]. Thus, both approaches should be studied separately. Another limitation of this study is that it does not include a placebo group, which may lead placebo effect bias.

The trial proposed herein is an original study in which for the first time antibiotics are compared with placebo after LC in cases of ACC. The CHART trial is a double blind RCT designed to evaluate the need and safety of antibiotic treatment after LC for mild or moderate ACC. The results of this trial will provide strong evidence for decision-making in this matter. This could avoid the unnecessary use of antibiotics after surgery, decreasing the incidence of associated adverse events, the emergence of bacterial resistance and treatment costs.

Trial status

The trial is ongoing and patient recruitment was started in January 2014.

Funding statement

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

The concept of the study derived from MDS. This study was designed by PP, JG, AD and MDS. The article was written by PP, JPC and MDS. DG performed the sample size calculation and planned the statistical analyses. PP, AD, JG, JG, JPC, DG, LB, OM, FA, RSC, MP, GA, VA, EDS, RSC, JP and MDS are involved in trial implementation and critically revised the manuscript. All authors have read and approved the manuscript.

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Footnotes

Abbreviations

ACC: acute calculus cholecystitis; AIDS: acquired immunodeficiency syndrome; AMC: amoxicillin-clavulanic acid; CEPI: research projects evaluating committee; CHART: cholecystectomy antibiotic randomized trial HIBA; Hospital Italiano de Buenos Aires; LC: laparoscopic cholecystectomy; RCT: randomized controlled trial; TP: treatment pack.

References:

1. Yusoff IF, Barkun JS, Barkun AN. Diagnosis and management of cholecystitis and cholangitis. Gastroenterology clinics of North America 2003;**32**(4):1145-68

2. Strasberg SM. Clinical practice. Acute calculous cholecystitis. The New England journal of medicine 2008;**358**(26):2804-11 doi: 10.1056/NEJMcp0800929[published Online First: Epub Date]|.

3. Mazeh H, Mizrahi I, Dior U, et al. Role of antibiotic therapy in mild acute calculus cholecystitis: a prospective randomized controlled trial. World J Surg 2012;**36**(8):1750-9 doi: 10.1007/s00268-012-1572-6[published Online First: Epub Date]|.

4. Yoshida M, Takada T, Kawarada Y, et al. Antimicrobial therapy for acute cholecystitis: Tokyo Guidelines. Journal of hepato-biliary-pancreatic surgery 2007;**14**(1):83-90 doi: 10.1007/s00534-006-1160-y[published Online First: Epub Date]|.

5. Yokoe M, Takada T, Strasberg SM, et al. TG13 diagnostic criteria and severity grading of acute cholecystitis (with videos). Journal of hepato-biliary-pancreatic sciences 2013;**20**(1):35-46 doi: 10.1007/s00534-012-0568-9[published Online First: Epub Date]|.

6. Kanafani ZA, Khalife N, Kanj SS, et al. Antibiotic use in acute cholecystitis: practice patterns in the absence of evidence-based guidelines. The Journal of infection 2005;**51**(2):128-34 doi: 10.1016/j.jinf.2004.11.007[published Online First: Epub Date]|.

7. Fuks D, Cosse C, Regimbeau JM. Antibiotic therapy in acute calculous cholecystitis. Journal of visceral surgery 2013;**150**(1):3-8 doi: 10.1016/j.jviscsurg.2013.01.004[published Online First: Epub Date]|.

8. Johannes CB, Ziyadeh N, Seeger JD, et al. Incidence of allergic reactions associated with antibacterial use in a large, managed care organisation. Drug safety 2007;**30**(8):705-13

9. Clavien PA, Barkun J, de Oliveira ML, et al. The Clavien-Dindo classification of surgical complications: five-year experience. Annals of surgery 2009;**250**(2):187-96 doi: 10.1097/SLA.0b013e3181b13ca2[published Online First: Epub Date]|.

10. Yildiz B, Abbasoglu O, Tirnaksiz B, et al. Determinants of postoperative infection after laparoscopic cholecystectomy. Hepato-gastroenterology 2009;**56**(91-92):589-92

11. Agabiti N, Stafoggia M, Davoli M, et al. Thirty-day complications after laparoscopic or open cholecystectomy: a population-based cohort study in Italy. BMJ open 2013;**3**(2) doi: 10.1136/bmjopen-2012-001943[published Online First: Epub Date]|.

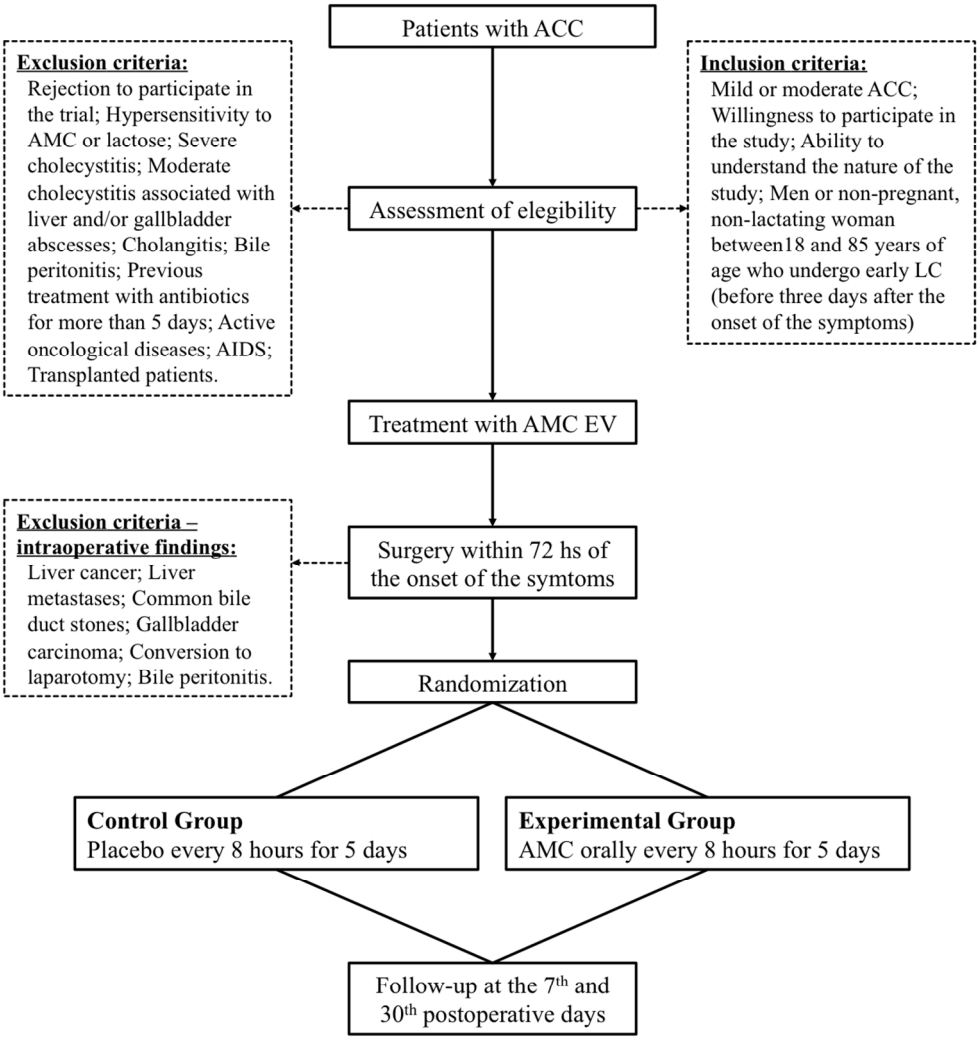
12. Jatzko GR, Lisborg PH, Pertl AM, et al. Multivariate comparison of complications after laparoscopic cholecystectomy and open cholecystectomy. Annals of surgery 1995;**221**(4):381-6

13. Lujan JA, Parrilla P, Robles R, et al. Laparoscopic cholecystectomy vs open cholecystectomy in the treatment of acute cholecystitis: a prospective study. Archives of surgery 1998;**133**(2):173-5

14. Lau WY, Yuen WK, Chu KW, et al. Systemic antibiotic regimens for acute cholecystitis treated by early cholecystectomy. The Australian and New Zealand journal of surgery 1990;**60**(7):539-43

15. Regimbeau JM, Fuks D, Pautrat K, et al. Effect of postoperative antibiotic administration on postoperative infection following cholecystectomy for acute calculous cholecystitis: a randomized clinical trial. Jama 2014;**312**(2):145-54 doi: 10.1001/jama.2014.7586[published Online First: Epub Date]|.

16. Coccolini F, Catena F, Pisano M, et al. Open versus laparoscopic cholecystectomy in acute cholecystitis. Systematic review and meta-analysis. International journal of surgery 2015;**18**:196-204 doi: 10.1016/j.ijsu.2015.04.083[published Online First: Epub Date]|.



Trial design chart. ACC, acute calculus cholecystitis; AIDS, acquired immunodeficiency syndrome; AMC, amoxicillin-clavulanic acid; EV, endovenous; LC, laparoscopic cholecystectomy.
451x520mm (72 x 72 DPI)

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The diagnostic criteria and severity assessment of acute cholecystitis have been well established in the 2007 Tokyo Guidelines, updated in 2013. According to these guidelines, ACC is classified as mild (Grade I), moderate (Grade II) and severe (Grade III). Severe acute cholecystitis is associated with at least one organ dysfunction. Moderate acute cholecystitis is associated with any of the following conditions: elevated WBC count (18,000/mm3); palpable tender mass in the right upper abdominal quadrant; duration of complaints for more than 72 hours; marked local inflammation (gangrenous cholecystitis, pericholecystic abscess, hepatic abscess, biliary peritonitis, emphysematous cholecystitis). Mild acute cholecystitis does not meet the criteria of any of the formers. It can also be defined as an acute cholecystitis in a healthy patient with no organ dysfunction with only mild inflammatory changes in the gallbladder[5].

While laparoscopic cholecystectomy (LC) is the gold standard treatment of mild and moderate forms of ACC, the need for antibiotic therapy after surgery continues to be a matter of debate. There is a lack of evidence regarding duration and type of

antimicrobial therapy after surgery[2-6]. The updated Tokyo Guidelines propose to administer antibiotics only up to 24 hours after surgery for mild ACC and 4-7 days in moderate or severe cases[4]. It has been suggested that a beta-lactam monoscheme (i.e. amoxicillin/clavulanic acid [AMC]) would be adequate in patients with mild and moderate cholecystitis without intraoperative complications such as bile peritonitis, cholangitis, gallbladder perforation or abscesses[4-7]. However, the real benefits of its use in these situations have not been well studied. Antibiotics are associated with common adverse effects such as allergic reactions and digestive intolerance (nausea, vomits and diarrhea). Nowadays, there is a clear tendency towards the rational use of antibiotics in order to prevent bacterial resistance. Amoxicilin has been associated with a 7-8% incidence of toxicodermia, 1% of allergy reactions and a very low incidence of anaphylactic shock (0.01-0.04% with the use of penicillin) [8]. Hence, we decided to conduct a RCT in patients undergoing LC for mild and moderate ACC, randomizing patients to receive AMC or placebo after surgery. The primary objective of the present trial is to assess whether antibiotic treatment after LC in mild or moderate ACC reduces the incidence of postoperative infectious complications. The hypothesis is that postoperative antibiotics have no positive impact in patient's outcome and, therefore, should not be indicated in this subset of patients.

Methods and analysis

Trial design, setting and randomization

The CHART trial is a randomized, controlled and blind to patient, investigator and data analysts study, which compares antibiotic treatment after LC due to mild and moderate ACC versus no antibiotic treatment. From February 2014, surgeons initiated this study (protocol version 1.0) at Hospital Italiano de Buenos Aires (HIBA). This is a teaching

hospital affiliated to the University of Buenos Aires Medical School and the HIBA University Medical School.

All patients admitted with acute calculous cholecystitis will receive parenteral hydration, gastric protection with proton pump inhibitors, analgesics and intravenous treatment with AMC. This treatment is continued until the operation. Surgery will be performed within the first 5 days after admission. Those patients who worsen during the waiting time will be explored as soon as possible. Potential complications (such as bile peritonitis, cholangitis, gallbladder perforation or abscesses) or evidence of greater severity of cholecystitis may occur and this can only be diagnosed during surgery. These patients will not be eligible for randomization and will be dismissed from the statistical analysis. Nevertheless, this group will be considered in the final flow chart.

After screening for eligibility and informed consent is obtained, patients will be randomized in a 1:1 ratio into one of the following study groups (Figure 1):

• Antibiotic treatment

• Placebo

In summery, patients are recruited prior to surgery but are randomized only after surgery, once the investigators confirm that no exclusion criteria are present intraoperatively.

Patients will be randomized using the online randomizer provided by the Hospital Italiano Statistics Department (http://protocolos.hospitalitaliano.org.ar). This randomizer provides a list with a sequence of numbers from 1 to 300; each one randomly assigned to one of the study groups. Patients will be assigned to each number in order according to the moment they enter the protocol. Neither the researchers nor the patients will have knowledge of the assigned treatment until the end of the study. Each Treatment Pack (TP) will have a code to retrospectively help identify which group of

treatment the patient was assigned to. Each TP contain capsules for a 5-day-treatment to be administered 3 times per day. The capsules will be provided by the Hospital Italiano de Buenos Aires (HIBA) Central Pharmacy according to the randomization list. The antibiotic and placebo capsules will be packaged and labelled identically. These capsules will be made of insipid gelatin material and will have the same colour.

Trial organization

Trial population and patient recruitment

All consecutive patients with the new diagnosis of mild or moderate ACC according to the Revised Tokyo Guidelines[5] admitted to the HIBA will be screened for eligibility to be enrolled in the CHART trial.

Patients will be approached for randomized inclusion if they meet each of the following inclusion criteria: diagnosis of mild or moderate ACC; willingness to participate in the study; ability to understand the nature of the study and what will be required of them; men or non-pregnant, non-lactating woman between 18 and 85 years of age who undergo early LC (before 3 days after the onset of the symptoms).

Exclusion criteria are: rejection to participate in the trial or the process of informed consent; hypersensitivity to AMC or lactose (used in placebo); severe ACC; moderate ACC associated with liver and/or gallbladder abscesses, cholangitis or bile peritonitis; intraoperative findings such as liver cancer, liver metastases, common bile duct stones or gallbladder carcinoma; conversion to laparotomy; previous treatment with antibiotics for more than 5 days; active oncological diseases; acquired immunodeficiency syndrome (AIDS); transplanted patients.

Trial interventions

All patients admitted to HIBA from February 2014 with mild or moderate AAC were invited to participate in the study. Surgeons from the hepatobliopancreatic section of the HIBA will recruit participants. Patients will receive parenteral hydration, gastric protection with protons pump inhibitors, analgesics and treatment with 1000 mg of AMC intravenously every 8 hours until surgery, which has to be performed within 5 days after admission. No extra dose of AMC will be administered during surgery.

If there are no intraoperative criteria for exclusion, patients will be randomly assigned to either group of intervention:

***Experimental group*: Antibiotic treatment after surgery**

Patients in the experimental group will receive 1000 mg of AMC orally every 8 hours for 5 days, immediately after the surgery.

***Control group*: Placebo treatment after surgery**

Patients in the control group will receive placebo orally every 8 hours for 5 days, immediately after the surgery.

Study objectives and endpoints

The primary objective of the present trial is to assess whether antibiotic treatment after LC in mild or moderate ACC reduces the incidence of postoperative infectious complications.

Primary endpoint

The primary efficacy endpoint is postoperative infectious complications, defined as any infection occurring within the first 30 postoperative days, classified according to Clavien-Dindo Classification[9]. After randomization patients will be followed-up for 30 days.

Secondary endpoints

- Length of hospital stay: number of days from admission to hospital discharge.
- Readmission: need of readmission due to postoperative complications that require hospital care (hydration, intravenous antibiotics, percutaneous drainage, surgical treatment).
- Reintervention: need of surgical treatment under general anesthesia or percutaneous procedure in complicated patients.
- Overall mortality: deaths occurred in the first postoperative month.

Trial implementation

Inclusion, evaluation and follow-up

Patients will be screened according to the eligibility criteria and asked for written informed consent. Afterwards, they will be allocated randomly to each of both study groups.

Study schedule

The evaluation schedule for all patients will be as follows:

Stage 1= Every patient included in the protocol will be registered in a sheet containing personal information and data on the primary and secondary endpoints.

TP will be administered during the five postoperative days. Each patient will receive a medicament control sheet, where they will register every dose. On days 7 and 30, patients will be monitored in the outpatient's office. Patients will be given contact telephone numbers in case they have any concern or need to report any event during follow-up. All data collected will be registered in the follow-up sheet.

Stage 2= During this stage, researchers will carry out a statistical analysis of the analyzed variables and their relations.

Sample size

We hypothesized that the absence of postoperative antibiotic treatment would not be inferior to receiving antibiotics after surgery for the development of surgical site and distant infections after cholecystectomy. Our sample size calculation was based on published data[10-13] and on an expected postoperative infection rate in the antibiotic group of 3%. Assuming a non-inferiority margin of 5%, a one-tailed alpha error of 5% and a power of 80% to reject this null hypothesis, we estimated that the required sample size would be 150 cases in each group.

Monitoring

All data will be registered in follow-up sheets by the investigators. These sheets will be weekly exported to Microsoft Access® (version 2013, Microsoft Corporation, California, USA). The Research Projects Evaluating Committee (CEPI) of HIBA will audit this trial every 6 months. An interim analysis will be performed once 150 patients are recruited.

Statistical analysis

Confirmatory analysis

A non-inferiority design was chosen. The results will be analyzed on an intention-to-treat basis. The association between outcome and the assigned treatment will be evaluated using the CHI^2 TEST in discrete variables and ANOVA for continuous

variables. All data analysis will be performed using the SPSS® software package version 17.0 (SPSS, Chicago, Illinois, USA).

Clinical management and abandonment

Patients included are warned not to take medications from other doctors outside the study. In case a patient requires antibiotics for some reason, the blind will be revealed to ensure the proper treatment for this patient. This event will be registered and the patient will be considered in the statistical analysis.

Each patient is informed to be free to abandon the treatment at any time by informing the researchers. If the medical team or researchers consider that the patient is at risk due to the study, the patient will be removed and the doctors will provide feedback to the patient.

Damage and complications

If the patient presents any infectious complication during the postoperative stage or any sign of persistent infection such as leukocytosis (defined as a white blood cell count of 10,000/mm3 or more), fever over 38ºC (100.4ºF), hepatogram alterations, cholangitis or hepatic abscesses, the medical team will proceed to stop the administration of TP and decide which medical actions need to be taken according to each particular case. Any adverse event detected during outpatient monitoring will be registered and classified according to its severity into mild, moderate and severe:

1- Mild: transitory events that do not require special treatment. These events do not affect patient's daily life.

2- Moderate: events that interfere in the patient's daily routine that require minimal, local or noninvasive intervention.

3- Severe: medically significant, disabling or immediately life-threatening events that require hospitalization and/or urgent intervention.

Ethics and dissemination

Ethics approval

The CHART trial is conducted in line with the current national and international regulations: World Medical Association Declaration of Helsinki, Regulation 5330/07 ANMAT, the Standards of Good Practices ICH E6 and the laws and regulations of the country, providing the greatest protection of the patient. The trial protocol and informed consent sheets have been approved by the CEPI of HIBA (protocol Nº 2111). The CHART trial has been registered at Clinicaltrial.gov database (**ClinicalTrials.gov, Identifier:** NCT02057679).

Informed consent and confidentiality

In all cases, the participation in the study is voluntary and certified by the process of informed consent. The right to refuse to participate in the study will be respected at all times without any implications in the treatment of the patient disease. The antibiotics proposed correspond to the empirical initial scheme that is in use in our institution for patients with inflammatory/infectious hepato-biliary affections acquired in the community. All data collected will be treated with confidentiality and anonymously. Authorized personnel can only access the records of the study in compliance with the current legal regulation: National Law of Personal Information Protection No. 25.326 (Habeas Data Law).

All patients will be informed of the aims of the study, the possible adverse events, the procedures and possible hazards to which he/she will be exposed, and the mechanism of

treatment allocation. Furthermore, it is the responsibility of the investigator to explain the patients their duties within the trial. They will be informed about the strict confidentiality of their personal data, but that their medical records may be reviewed for trial purposes by authorized individuals other than their treating physician. Trial findings will be stored in accordance with local data protection law/ICH GCP-Guidelines and will be handled in the strictest confidence. For protection of these data, organizational procedures are implemented to prevent distribution of data to unauthorized people.

Dissemination

Anonymised results of the study will be published in a peer-reviewed journal, and will be presented at academic meetings and scientific conferences. Only the registered investigators will have access to the individual patient data.

Discussion

Although ACC is one of the most common diseases in general surgery, few trials have assessed the role of antibiotic therapy after LC. Most publications on the subject analyze the use of antibiotics after conventional procedures, or mix in the same design open and laparoscopic procedures.

In the late 1980s, Lau et al randomized 203 patients and compared a short course of 2 doses versus a long course of 7 days of cefamandole after early open cholecystectomy. They found that the short course was as effective as the long one in reducing postoperative infectious complications with the additional advantages of lower costs, risks of adverse events and length of hospital stay[14]. This was the first study to suggest that a reduction in the use of postoperative antibiotics may be possible.

However, this study is outdated given the many changes in bacterial resistance over time and the modern surgical therapies. In addition to these findings, Mazeh et al conducted a randomized controlled trial (RCT) in which they demonstrated that the addition of intravenous antibiotic treatment to supportive care has limited, if any, effect in patients with mild ACC[3].

Recently, Regimbeau et al. published a multicenter RCT in which patients admitted with mild and moderate ACC were randomized to antibiotics or no treatment after surgery[15]. To the author's opinion, the main limitation of this study is that it includes both conventional and laparoscopic approaches (15% open cholecystectomies and a 10% conversion rate). It has been widely demonstrated that one of the advantages of laparoscopic approach is that it is associated with less surgical side infections rate[16]. Thus, both approaches should be studied separately. Another limitation of this study is that it does not include a placebo group, which may lead placebo effect bias.

The trial proposed herein is an original study in which for the first time antibiotics are compared with placebo after LC in cases of ACC. The CHART trial is a double blind RCT designed to evaluate the need and safety of antibiotic treatment after LC for mild or moderate ACC. The results of this trial will provide strong evidence for decision-making in this matter. This could avoid the unnecessary use of antibiotics after surgery, decreasing the incidence of associated adverse events, the emergence of bacterial resistance and treatment costs.

Trial status

The trial is ongoing and patient recruitment was started in February 2014.

Funding statement

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests

No, there are no competing interests.

Authors' contributions

The concept of the study derived from MDS. This study was designed by PP, JG, AD and MDS. The article was written by PP, JPC and MDS. DG performed the sample size calculation and planned the statistical analyses. PP, AD, JG, JG, JPC, DG, LB, OM, FA, RSC, MP, GA, VA, EDS, RSC, JP and MDS are involved in trial implementation and critically revised the manuscript. All authors have read and approved the manuscript.

Acknowledgements

We thank the Central Pharmacy staff of the HIBA. The CHART trial is funded exclusively by the institutional/departmental sources.

Footnotes

Abbreviations

ACC: acute calculous cholecystitis; AIDS: acquired immunodeficiency syndrome; AMC: amoxicillin-clavulanic acid; CEPI: research projects evaluating committee; CHART: cholecystectomy antibiotic randomized trial HIBA; Hospital Italiano de Buenos Aires; LC: laparoscopic cholecystectomy; RCT: randomized controlled trial; TP: treatment pack.

References:

1. Yusoff IF, Barkun JS, Barkun AN. Diagnosis and management of cholecystitis and cholangitis. Gastroenterology clinics of North America 2003;**32**(4):1145-68

2. Strasberg SM. Clinical practice. Acute calculous cholecystitis. The New England journal of medicine 2008;**358**(26):2804-11 doi: 10.1056/NEJMcp0800929[published Online First: Epub Date]|.

3. Mazeh H, Mizrahi I, Dior U, et al. Role of antibiotic therapy in mild acute calculus cholecystitis: a prospective randomized controlled trial. World J Surg 2012;**36**(8):1750-9 doi: 10.1007/s00268-012-1572-6[published Online First: Epub Date]|.

4. Yoshida M, Takada T, Kawarada Y, et al. Antimicrobial therapy for acute cholecystitis: Tokyo Guidelines. Journal of hepato-biliary-pancreatic surgery 2007;**14**(1):83-90 doi: 10.1007/s00534-006-1160-y[published Online First: Epub Date]|.

5. Yokoe M, Takada T, Strasberg SM, et al. TG13 diagnostic criteria and severity grading of acute cholecystitis (with videos). Journal of hepato-biliary-pancreatic sciences 2013;**20**(1):35-46 doi: 10.1007/s00534-012-0568-9[published Online First: Epub Date]|.

6. Kanafani ZA, Khalife N, Kanj SS, et al. Antibiotic use in acute cholecystitis: practice patterns in the absence of evidence-based guidelines. The Journal of

infection 2005;**51**(2):128-34 doi: 10.1016/j.jinf.2004.11.007[published Online First: Epub Date]|.

7. Fuks D, Cosse C, Regimbeau JM. Antibiotic therapy in acute calculous cholecystitis. Journal of visceral surgery 2013;**150**(1):3-8 doi: 10.1016/j.jviscsurg.2013.01.004[published Online First: Epub Date]|.

8. Johannes CB, Ziyadeh N, Seeger JD, et al. Incidence of allergic reactions associated with antibacterial use in a large, managed care organisation. Drug safety 2007;**30**(8):705-13

9. Clavien PA, Barkun J, de Oliveira ML, et al. The Clavien-Dindo classification of surgical complications: five-year experience. Annals of surgery 2009;**250**(2):187-96 doi: 10.1097/SLA.0b013e3181b13ca2[published Online First: Epub Date]|.

10. Yildiz B, Abbasoglu O, Tirnaksiz B, et al. Determinants of postoperative infection after laparoscopic cholecystectomy. Hepato-gastroenterology 2009;**56**(91-92):589-92

11. Agabiti N, Stafoggia M, Davoli M, et al. Thirty-day complications after laparoscopic or open cholecystectomy: a population-based cohort study in Italy. BMJ open 2013;**3**(2) doi: 10.1136/bmjopen-2012-001943[published Online First: Epub Date]|.

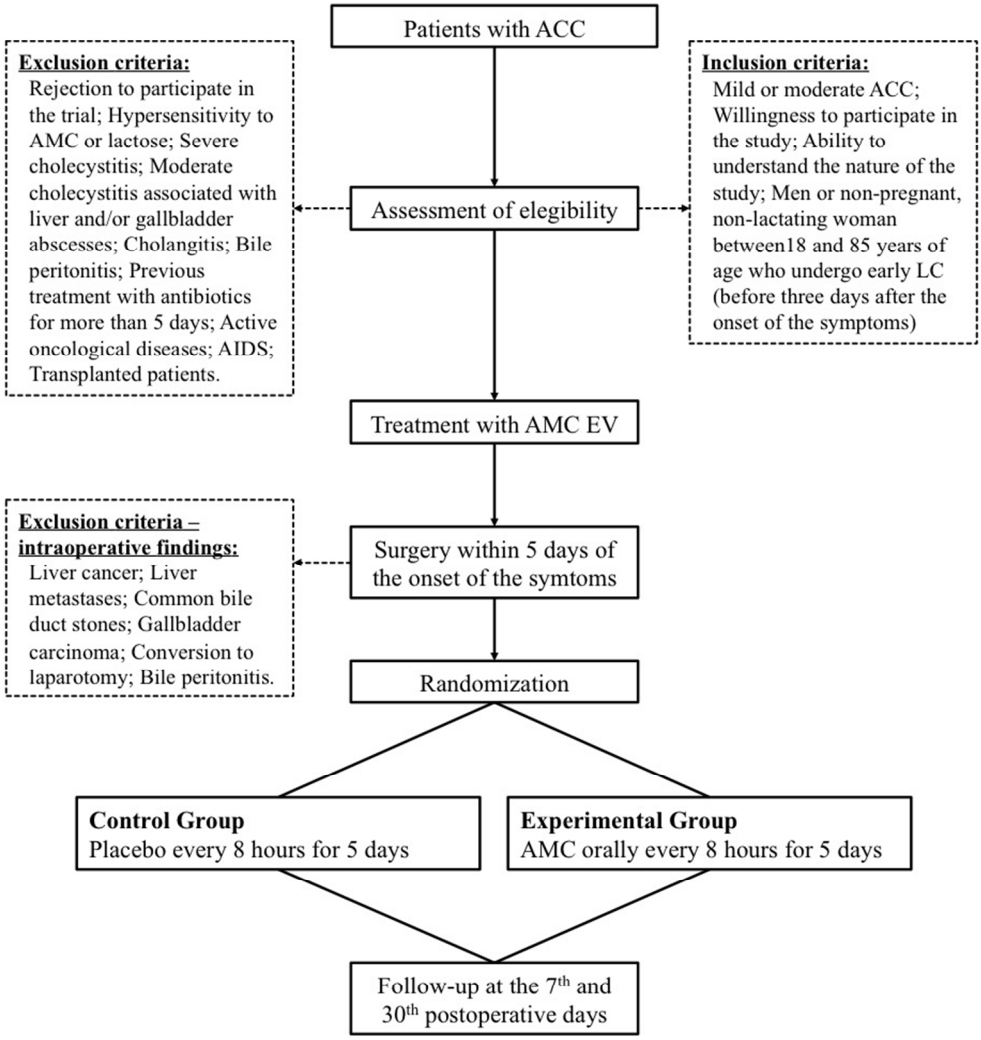
12. Jatzko GR, Lisborg PH, Pertl AM, et al. Multivariate comparison of complications after laparoscopic cholecystectomy and open cholecystectomy. Annals of surgery 1995;**221**(4):381-6

13. Lujan JA, Parrilla P, Robles R, et al. Laparoscopic cholecystectomy vs open cholecystectomy in the treatment of acute cholecystitis: a prospective study. Archives of surgery 1998;**133**(2):173-5

14. Lau WY, Yuen WK, Chu KW, et al. Systemic antibiotic regimens for acute cholecystitis treated by early cholecystectomy. The Australian and New Zealand journal of surgery 1990;**60**(7):539-43

15. Regimbeau JM, Fuks D, Pautrat K, et al. Effect of postoperative antibiotic administration on postoperative infection following cholecystectomy for acute calculous cholecystitis: a randomized clinical trial. Jama 2014;**312**(2):145-54 doi: 10.1001/jama.2014.7586[published Online First: Epub Date]|.

16. Coccolini F, Catena F, Pisano M, et al. Open versus laparoscopic cholecystectomy in acute cholecystitis. Systematic review and meta-analysis. International journal of surgery 2015;**18**:196-204 doi: 10.1016/j.ijsu.2015.04.083[published Online First: Epub Date]|.



Trial design chart. ACC, acute calculous cholecystitis; AIDS, acquired immunodeficiency syndrome; AMC, amoxicillin-clavulanic acid; EV, endovenous; LC, laparoscopic cholecystectomy.
330x381mm (72 x 72 DPI)

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	_____1_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	_____3_____
	2b	All items from the World Health Organization Trial Registration Data Set	_____3_____
Protocol version	3	Date and version identifier	_____6_____
Funding	4	Sources and types of financial, material, and other support	_____15_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	____1, 2, 15_____
	5b	Name and contact information for the trial sponsor	___not applicable_
	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	__not applicable__
	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)	__not applicable__

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4, 5
	6b	Explanation for choice of comparators	4, 5
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5, 6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7, 8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8, 9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	11, 12
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	10
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	11
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6–9

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	10
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	7
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7
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	7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	11
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10, 11
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	10, 11

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	_____11_____
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	_____11_____
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	__not applicable__
	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)	__not applicable__
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	_____10, 11____
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	_____10, 11____
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	_____10, 11____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	_____10, 11____
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	_____12_____
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	__not applicable__

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	_____13_____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	__not applicable__
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	_____13_____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	_____15_____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	_____13_____
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	_____11, 12____
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	_____13_____
	31b	Authorship eligibility guidelines and any intended use of professional writers	__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	__appendix_____
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__

*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.