

BMJ Open Acute uncomplicated appendicitis study: rationale and protocol for a multicentre, prospective randomised controlled non-inferiority study to evaluate the safety and effectiveness of non-operative management in children with acute uncomplicated appendicitis

Jane Xu,¹ Yingrui Cyril Liu,² Susan Adams,^{1,2} Jonathan Karpelowsky^{3,4}

To cite: Xu J, Liu YC, Adams S, *et al.* Acute uncomplicated appendicitis study: rationale and protocol for a multicentre, prospective randomised controlled non-inferiority study to evaluate the safety and effectiveness of non-operative management in children with acute uncomplicated appendicitis. *BMJ Open* 2016;**6**:e013299. doi:10.1136/bmjopen-2016-013299

► Prepublication history and additional material is available. To view please visit the journal (<http://dx.doi.org/10.1136/bmjopen-2016-013299>).

Received 5 July 2016
Revised 5 October 2016
Accepted 21 October 2016



CrossMark

For numbered affiliations see end of article.

Correspondence to
Dr Susan Adams;
susan.adams@unsw.edu.au

ABSTRACT

Introduction: This article presents an overview of a prospective randomised controlled non-inferiority study designed to evaluate the safety and effectiveness of non-operative management (NOM) with operative management in children with acute uncomplicated appendicitis (AUA). Here, we present the study protocol for this APRES study, a multicentre Australian study. The rationale and details of future analysis, in particular, non-inferiority calculations, cost-effectiveness, feasibility and acceptability of each intervention.

Design: A multicentre, prospective randomised controlled clinical trial, conducted in 2 Australian tertiary paediatric hospitals.

Participants: Children who meet the inclusion criteria of an age between 5 and 15 years and a clinical diagnosis of AUA will be invited to participate, and after consent will be randomised via a computer-based program into treatment groups. The study started in June 2016, and the target recruitment is 220 patients.

Interventions: Children in the control group will be treated with prophylactic antibiotics and appendectomy, and those in the intervention group will be treated with antibiotic therapy alone. Primary outcome measures include unplanned or unnecessary operation and complications at 30 days. Secondary outcomes include longer term complications within 1 year, length of stay, time off work and school analgesic requirements and cost.

Analysis: Data analyses will be on the intention-to-treat principle using non-inferiority analysis. Analysis will include the Pearson χ^2 test for categorical variables and independent sample t-test or Mann-Whitney test for continuous variables. Non-inferiority for NOM will be tested using 1-sided Wald tests with an α level of 0.05.

Ethics and dissemination: The research has been approved by the Human Research Ethics Committee of the Sydney Children's Hospital Network. In addition,

Strengths and limitations of this study

- One of the first, well-designed randomised controlled trial with a substantial sample size studying non-inferiority of non-operative management with operative management of appendicitis in the paediatric population.
- First study of this type conducted in Australia.
- A multicentre study.
- Non-blinded.
- May include patients without appendicitis, the diagnosis is clinical and left to the treating physician.

results will be reported through academic journals, seminars and conference presentations.

Trial registration numbers: NCT02795793; ACTRN12616000788471.

INTRODUCTION

Appendectomy for acute appendicitis is one of the most commonly performed paediatric emergency operations in Australia, accounting for 8.2% of all general paediatric operations performed at a major tertiary paediatric hospital in Sydney in 2009.¹ Most appendectomies are for acute uncomplicated appendicitis (AUA). Standard treatment of management has remained largely unchanged since its introduction in the late 19th century, largely because of the assumption that AUA progresses to perforation should an operation be withheld.² However,

appendicectomy via laparoscopic or open approach is not without its risks. Postoperative complications following appendicectomy, including wound infection and ileus, have been reported to be between 1.9% and 8.8%.^{3–4} In addition, 2.8% of patients require further admissions for appendicectomy-related adhesive small bowel obstruction.⁵ Despite recent improvements on medical imaging techniques, 6–15% of all appendicectomies are performed on patients with histologically normal appendices.^{6–7}

Non-operative management (NOM) with antibiotics has been increasingly accepted as mainstay therapy for many intra-abdominal infections. Children with appendicitis complicated by perforation, abscess or phlegmon formation can be primarily treated non-operatively with antibiotic therapy, with or without percutaneous drainage.^{8–10}

Prospective studies, systematic reviews and meta-analyses have demonstrated that antibiotics are a safe and effective treatment for AUA in adults.^{11–19} The Appendicitis Acuta (APPAC) multicentre, open-label, non-inferiority, randomised controlled trial (RCT) in adults reported a significantly lower overall complication rate of 2.8% in the NOM group, compared with 20.5% in patients who received operative management (OM). Importantly, only 7 of 256 patients in the non-operative group had progression to complicated appendicitis during the 1-year follow-up period.¹⁹

There is growing evidence that NOM is also safe and effective in children. Currently, there has been one published randomised pilot study²⁰ and several cohort studies^{21–32} that have shown a relatively low risk of complications and subsequent appendicitis following NOM. The pilot RCT is limited by its small sample size and short follow-up period. The other studies, while limited by study design, demonstrated a promising initial treatment success rate of 58–100%, a considerably shortened recovery time, and improved quality of life scores when compared with the OM.^{20–32} It is not known how amenable parents and carers will be to the offer of NOM to treat AUA in their child. Authors of previous papers supported the further evaluation of NOM with a well-designed prospective RCT with larger sample sizes and robust randomisation methods, assessing the non-inferiority of NOM in clinically diagnosed children with AUA.

This project is designed as a non-inferiority study to assess the safety and effectiveness of NOM in AUA, with secondary analysis of length of stay, time off work and school, longer term complications and costs. The acceptability and feasibility of offering this alternative treatment will also be assessed.

Study objectives

The null hypothesis is that NOM of clinically diagnosed likely AUA in children is inferior to OM in terms of safety and efficacy.

The primary objective is to determine the safety and efficacy of non-operative, antibiotic management of clinically diagnosed likely AUA in children.

The secondary objectives are

1. To compare the safety and efficacy of NOM of clinically diagnosed likely AUA with OM in children.
2. To assess the cost-effectiveness of NOM of clinically diagnosed likely AUA against OM in children.
3. To assess the feasibility and acceptability of NOM of appendicitis in children.

METHODS AND ANALYSIS

Trial design

The APRES trial is designed as a multicentre prospective, open-label, non-inferiority, RCT with two parallel groups (OM and NOM). Previous studies suggest NOM is potentially as effective as OM, but as there is no suggestion that it is superior, along with the fact that blinding or placebo is not possible or ethical, a non-inferiority design was chosen.³³

Study setting

To allow a robust non-inferiority design with a constant non-inferiority margin, the baseline negative appendicectomy rate at the trial sites must be similar. The study settings are the two tertiary hospitals in the Sydney Children's Hospital network (SCHN): The Children's Hospital at Westmead (CHW; site 1) and Sydney Children's Hospital, Randwick (SCH; site 2). Each year, the SCHN provides care for ~92 000 emergency presentations, and ~600 cases of appendicitis. Both centres report an average negative appendicectomy rate of 10% in their Children's Hospitals Australasia Clinical Indicators. These well-resourced hospitals deliver a complex and comprehensive range of care for ill and injured children and adolescents throughout, and beyond the state of New South Wales.

Eligibility criteria

All children between 5 and 16 years of age referred to paediatric surgical team for suspected acute appendicitis will be assessed by duty surgical registrar for possible inclusion in the study.

Inclusion criteria

Patients eligible for the trial must comply with all the following prior to randomisation:

1. Age between 5 and 15 years;
2. Clinical diagnosis by at least one paediatric surgeon of AUA based on a combination of clinical, laboratory and/or imaging findings; that before the study would have led to the decision to recommend appendicectomy.

Exclusion criteria

Children will be excluded from the study if one or more of the following is assessed to be present by the paediatric surgical team:

1. A diagnosis of perforated or complicated appendicitis (eg, peritonitis, appendiceal mass) is made on the basis of clinical, laboratory and/or imaging findings;
2. Previous non-operative treatment of acute appendicitis;
3. Age younger than 5 years or older than 16 years;
4. Known intolerance or allergy to piperacillin with tazobactam;
5. Known history of inflammatory bowel disease, or other chronic abdominal pain syndrome;
6. Known concurrent significant illness;
7. Unable to obtain informed consent from parents or guardian;
8. Known to have a cognitive impairment, an intellectual disability or mental illness that would impair participation.

Recruitment

Prior to enrolment and randomisation, eligible children will be approached by one of the investigators or the duty surgical registrar as their delegate. Where possible, the recruiter will not be part of the managing surgical team. The study will be explained to the child and parent/carer and the information sheet provided (see online supplementary appendix 1). Informed written consent for participation will be obtained from the parent/carer for those who wish to enrol.

Retention

The participant's free and voluntary involvement will be stressed at the time of recruitment. Where possible, recruitment will be by an investigator who is not part of their clinical care team. The patients will be informed at enrolment that their decision whether or not to take part or continue in the study will not affect the standard and availability of their medical care in any way. The participant and family will also have the contact number of the ethics committee should they have any concerns. There is no proposed payment or reimbursement for participants.

Participants withdrawn from the trial will be excluded from the study. All collected data from these patients will not be in the statistical analyses. The total number of participants withdrawn from the trial will be reported at the end of the study, but all the rest of the data will be kept confidential. Treatment and follow-up will be resumed as treating paediatric surgeon's normal practice. Withdrawn participants will be replaced with new recruitment until the target sample size is reached.

Allocation

Opaque envelopes based on a computer-generated randomisation will be used to allocate enrolled patient to treatment groups (OM and NOM). The duty registrar will perform the randomisation. An allocation ratio of 1:1 will be made via weighted minimisation using the following criteria: age (5–8 or 9–16 years), gender (male or female) and duration of symptoms (<48 or >48 hours).

Patient, family and the treating paediatric surgical team will be informed about randomisation result prior to initiation of treatment. Because of the nature of the interventions being evaluated, there will be no blinding in this study

Participant time line

Children allocated to OM may receive preoperative antibiotic prophylaxis as clinically indicated. Appendectomy will be performed laparoscopically or open, according to the surgeon's standard practice. Postoperative antibiotic treatment will be determined on the basis of intraoperative findings in accordance with the institutional practice (figure 1, table 1). The appendix specimen will be examined by a paediatric pathologist, and the formal histopathology report will be recorded.

Children in the NOM group will receive intravenous piperacillin with tazobactam (Tazocin) 100 mg/kg/dose every 8 hours for at least 24 hours. They will be observed and reassessed within 24 hours of randomisation. A further 24 hours of intravenous piperacillin with tazobactam therapy will be offered to children who are no worse but have not improved sufficiently for discharge (eg, ongoing fever or pain). A clinical decision will be made by the attending surgeon to offer OM if a patient's condition deteriorates at any time, or if a patient has failed to improve after 48 hours of intravenous antibiotic therapy. Once the patient is clinically improving and tolerating oral intake, the antibiotic regimen will be changed to oral amoxicillin plus clavulanic acid (augmentin) 22.5 mg/kg/dose twice per day to complete a total 7-day course of antibiotics. Oral ciprofloxacin 15 mg/kg/dose two times per day and oral metronidazole 10 mg/kg/dose two times per day will be offered to children who are known to have an intolerance or allergy to amoxicillin or clavulanic acid.

Children who are afebrile for 24 hours, mobile, tolerating a light diet and comfortable on oral analgesia will be fit for discharge. These discharge criteria apply to both groups.

Discharge instructions will advise that children with recurrent symptoms of appendicitis or symptoms of other complications at any time present to the emergency department.

To monitor patients' progress postdischarge, all participants will be seen in the outpatient clinic at 4–6 weeks after discharge as per standard practice, and a telephone interview will also be conducted at 1, 2 weeks, 3, 6 and 12 months after discharge.

OUTCOMES

Primary outcome measures

The primary outcome for the study is the treatment efficacy for NOM and OM in AUA based on the following within 30 days of randomisation:

1. Unplanned or unnecessary operation within 30 days of randomisation. An unplanned operation is

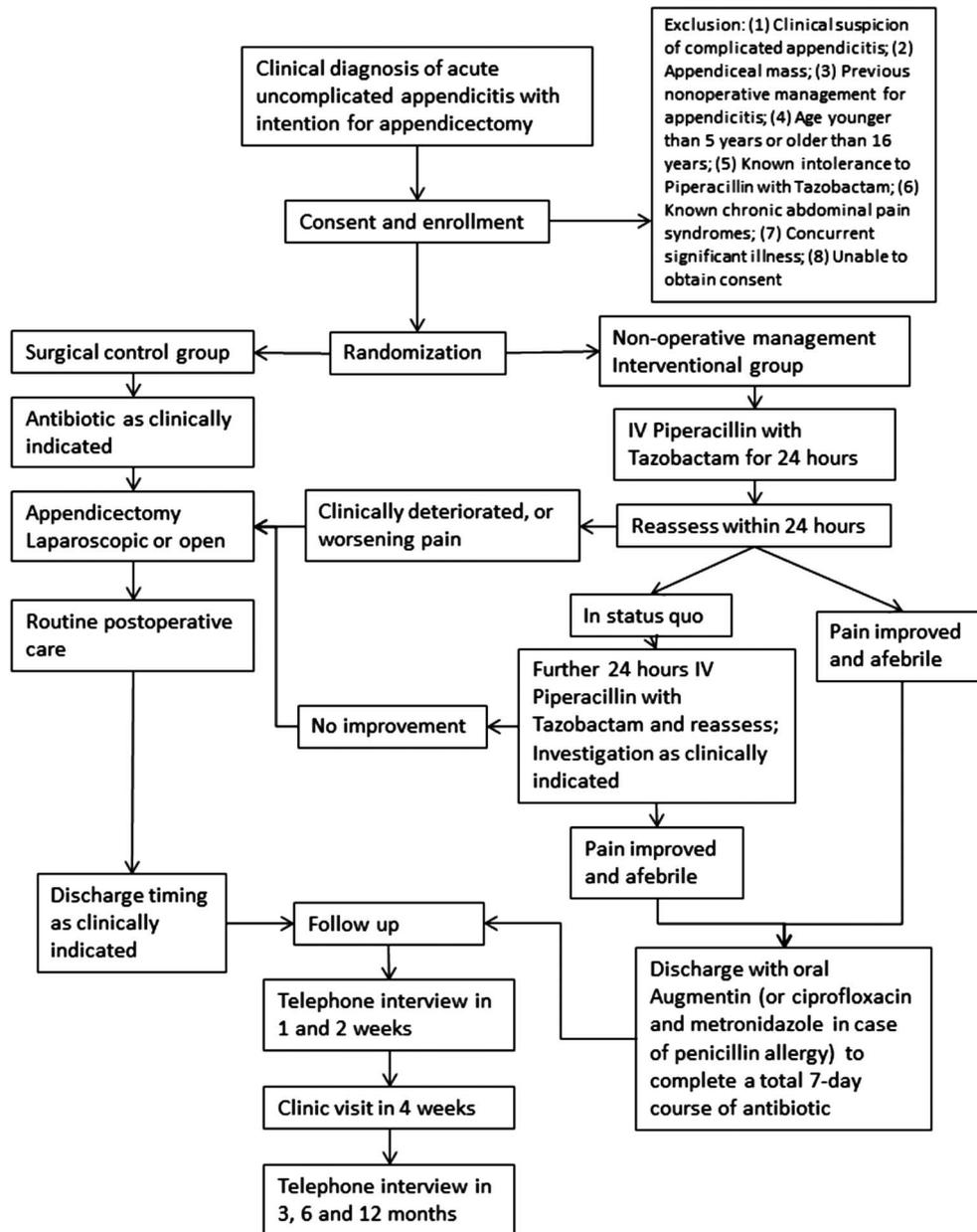


Figure 1 Study design diagram and participant timeline.

defined as an operation that occurs in a child that has completed randomisation and was allocated to the NOM group, or required an additional operation after initial appendicectomy in the OM group.

An unnecessary operation within 30 days of randomisation is defined as an operation (appendicectomy) that occurs in a child whose appendix does not show histological evidence of inflammation. This applies whether the appendicectomy is conducted as the initial operation in the group randomly allocated to surgery or whether it is a subsequent operation in the group initially allocated to no surgery.

This outcome is designed to account for the negative appendicectomy rate and extra operations that may occur in the OM group, as well as operations that occur in children that ‘fail’ NOM, all of which are accounted for in the non-inferiority calculation.

2. Complications, including any of the following within 30 days of randomisation:

Structural problems:

- ▶ Appendiceal perforation
- ▶ Bowel adhesions
- ▶ Bowel obstruction

Infections:

- ▶ Surgical site infection(s)
- ▶ Peritonitis
- ▶ Abscess or phlegmon formation
- ▶ Sepsis

Secondary outcome measures

The secondary outcomes for this study are:

1. Unplanned or unnecessary operation, or complications (as stated above) at 6 and 12 months postrandomisation.

Table 1 Standard care and additional to standard care procedures

Procedure	Timing	Dose, frequency and/or duration
Standard care		
Appendectomy laparoscopic or open	During admission	Once only
Preoperative antibiotic	During admission	Once only
Postoperative antibiotic	During admission and/or after discharge	As clinically indicated
Follow-up visit	4 to 6 weeks after discharge	Once only
Additional to standard care		
Intravenous piperacillin with tazobactam	During admission	100 mg/kg/dose every 8 hours for at least 24 hours up to 48 hours
Appendectomy laparoscopic or open	During admission when patient failed to respond to antibiotic therapy	None, or once only
Oral amoxicillin plus clavulanic acid	On discharge	22.5 mg/kg/dose twice per day to complete a total 7-day course of antibiotics
Oral ciprofloxacin and metronidazole	On discharge for patient allergic to augmentin	15 mg/kg/dose two times per day, and 10 mg/kg/dose two times per day, respectively, to complete a total 7-day course of antibiotics
Telephone interview	1, 2 weeks, 3, 6 and 12 months after discharge	5–10 min each interview. 5 times in total

- Length of primary hospital stay from time of randomisation to discharge in hours.
- Treatment-related complications.
- Readmission and emergency department presentation within 12 months.
- Cost of treatment in dollars—calculated at 1-year postrandomisation. It will be based on fees registered in Medicare Benefits Schedule (MBS), Pharmaceutical Benefits Scheme (PBS) and institution standard predetermined admission costing. It is calculated as a fee per day of in-hospital care, a fee for use of the operating theatre, the cost of a course of intravenous and oral antibiotics and the cost for total analgesic use. Cost for any additional admission will be calculated the same way when it is applicable.
- Days before return to school from time of randomisation.
- Days before return to normal activities from time of randomisation.
- Total analgesia requirement (types, routes and mg/kg).
- Antibiotic-associated side effects (eg, rash, vomiting, diarrhoea or colitis).
- Clinical outcomes of imaging-confirmed versus other suspected appendicitis in each group.

Sample size based on the reported postappendectomy complication rate of 1.9–8.8%^{3 4} and negative appendectomy rate of 6–15%,^{6 7} we would expect a treatment efficacy of 90% in the control OM group. Based on the reported treatment efficacy of 63–73%^{15 19} in adults treated with NOM and 58–100% in children,^{20–32} we would expect a possible difference of treatment efficacy between the control and treatment group to be between 15% and 25%. Thus, the failure rate in the OM group is assumed to be 10% and a failure rate of 25% or

more in the antibiotic group would be considered unacceptably high. For the non-inferiority study, the null hypothesis is that the antibiotic treatment is inferior and we wish to have an 80% power at 5% significance to rule out inferiority if the failure rate difference is 15% or lower (assuming the stated estimate of 10% failure rate in the surgery group). This requires a sample size of ~80 per group; however, we plan to recruit 110 patients per group to allow for up to 25% loss to follow-up. Each study site treats ~300 cases of appendicitis each year (600 in total) of which ~60% will be uncomplicated, resulting in a total of 360 eligible cases. Patient enrolment started in June 2016, and assuming a recruitment rate of 30%, we would recruit 110 per annum, thus aiming to recruit over a period of 2–3 years.

Data collection methods

The study will use the web-based application Research Electronic Data Capture (REDCap)³⁴ to record outcome variables for inpatient events, follow-up telephone calls and clinic visits. Data will be entered each day by the treating team and checked for completion and accuracy by one of the investigators. Data will then be entered in to an excel spread sheet and accuracy checked by two investigators.

Data management

The hard copies will be stored securely in a locked office and the soft copies on a password-protected REDCap database.

Statistical methods

The main analyses will be based on the intention-to-treat principle, but intention-to-treat and per-protocol analyses will be performed. The intention-to-treat population will include all randomised participants who start

on a treatment, excluding consent withdrawals. The per-protocol population will include all participants who complete the study at 1-year follow-up. A non-inferiority analysis will be performed to compare the primary and secondary outcomes. Based on current adult literature, the treatment efficacy difference between operative and non-operative treatment is about 25–35%.^{11–19} The most recent RCT in adults used 25% as its non-inferiority margin.¹⁹ In children, a 10% failure rate of NOM has been noted in the pilot study.²⁰ Thus, a non-inferiority margin of 15% will be used in this study.

Categorical variables will be characterised using frequencies and percentages. Statistical significance for categorical data will be tested using the Pearson χ^2 test. Continuous variables will be characterised as means and SDs or medians and IQR for non-parametric data. Differences between groups for normally distributed variables will be tested using the independent sample t-test. The Mann-Whitney test will be used for variables not normally distributed. Non-inferiority for NOM will be tested using the one-sided Wald tests with an α level of 0.05. Statistical analyses will be performed using the SPSS Statistics Program.

The predetermined power (1– β) is 80% for this study.

The total number of consent withdrawals from the study after randomisation will be reported but will be excluded from the final analysis.

MONITORING

Interim analysis, auditing, harms and adverse event reporting

Monitoring for safety will occur to detect any unacceptably high levels of complications or adverse events. Primarily, this is to monitor the occurrence of progress to complicated appendicitis in the intervention (NOM) arm, but other adverse events will also be monitored. To do this, a formal independent modified Data and Safety Monitoring Board (DSMB) will be convened for the study.

The DSMB will consist of three senior clinicians—one paediatrician, one surgeon and one infectious diseases specialist—none of whom are involved in recruitment or as investigators. Ad hoc specialists may be invited by the DSMB to participate as non-voting members at any time if additional expertise is desired. The chief investigator will provide the DSMB with:

- ▶ Interim/cumulative data from each centre;
- ▶ Recruitment and retention rates;
- ▶ Any protocol violations;
- ▶ Any adverse events and other unintended effects of the trial.

The DSMB will look at ongoing issues of participant recruitment, conduct of the trial and safety of participants and alert the investigators of concerns. Once assembled, the DSMB will revise their guidelines early in the study and they are at liberty to request additional information beyond what is described in the protocol at any time throughout the study.

The DSMB will be convened prior to the first recruitment and meet regularly throughout the trial.

The main perceived concern in this study is the potential increased risk of perforated appendicitis developing in patients in the NOM group. Other potential adverse events include prolonged hospital stay, operative complications, recurrent appendicitis, pain issues and antibiotic complications. Other adverse events unrelated to the trial may occur as is the case with any clinical situation. In order to minimise these risks, the protocol requires close clinical monitoring while in hospital, with clear criteria for cross over to OM in the NOM group. Other clinical issues that may arise will be monitored and managed by the treating team as is usual practice. Patients will be discharged with clear instructions on when to seek further medical attention. In addition, the planned telephone and clinic follow-up will actively seek information about complications or adverse events which will be managed as per usual clinical practice.

The investigating team will monitor the study progress, including adverse events with monthly meetings. The proceeds of these meetings will be provided to the DSMB along with a specific report on complications and adverse events experienced. Any interim serious adverse events reported spontaneously by the participant or observed by the investigators or staff will be documented and reported immediately to the chief investigator, who will inform the DSMB within 24 hours. Any concerns of the DSMB will be immediately discussed with the investigators, and reported directly to the Human Research Ethics Committee (HREC). The board may recommend trial termination or suspension pending an HREC review.

DISSEMINATION

Protocol amendments

Protocol amendments will be requested through the SCHN HREC. These changes will be communicated to the DSMB. Any material difference this makes to the participants in terms of what is required of them or what is consented to will be communicated to them with renewed consent sought where appropriate. Trial registries will be updated and material amendments noted in any subsequent publications.

Confidentiality

Hard copies of trial documentation, consent and data will be kept in a locked hospital office. Computer records will be kept on password-protected firewalled hospital servers. Data will be deidentified by using a master sheet that records name and MRN and study number. The data collection sheet will only contain study number as an identifier. The master sheet will be stored separately as a separate computer file or as a separate hard copy in a separate filing cabinet. In accordance with the HREC requirements for clinical trials on children, all information will be securely archived at the completion date for 15 years or until the youngest

participant turns 25 years, whichever is latest. For disposal, paper-based information will be securely shredded. Computer-based information will be securely deleted.

No extra bloods or tissue samples will be stored beyond that required for usual clinical care. Nor will any videos, photographs or images will be collected from patients.

Ancillary and post-trial care

Any post-trial care required will be provided by the admitting surgeon.

Dissemination policy

The trial is registered on ClinicalTrials.gov and ANZCTR, both of which have open access. The participant information includes a flow sheet that summarises the study plan. The study findings will be presented in a report which will be submitted for publication in a relevant peer-reviewed journal to ensure dissemination to relevant healthcare professionals. Findings may also be submitted for presentation at local meetings or conferences. The final report will be made available to trial participants via the investigators. The participant-level data set may be made available for meta-analyses pending relevant HREC approval.

EXPECTED OUTCOMES AND SIGNIFICANCE OF THE RESEARCH PROJECT

This project will be the first Australian study comparing NOM with OM for AUA in the paediatric setting, in addition to one of the first well-designed RCTs in this area. This study and its findings will provide essential information on the utility of NOM in children with AUA, and yields potential benefits for the wider community as well. These include decreased total treatment cost, shortened length of hospital stay, reduced days of sick leave for participants and carer leave as well as a non-inferior alternative option for those unfit for surgery. The potential for avoiding an operation also includes reduced degree and duration of pain, reduced rate of complications from an appendicectomy, reduced negative appendicectomy rate, expedited return to school and other normal activities.

Author affiliations

¹The School of Women's and Children's Health, The University of New South Wales, New South Wales, Australia

²Department of Paediatric Surgery, Sydney Children's Hospital, Randwick, New South Wales, Australia

³Division of Child and Adolescent Health, The University of Sydney, Sydney, New South Wales, Australia

⁴Department of Paediatric Surgery, The Children's Hospital at Westmead, Sydney, New South Wales, Australia

Contributors SA and JK initiated the project, and are the chief investigators. After a series of meetings and literature review, YCL drafted the protocol which was refined by SA and JK with input from the SCHN HREC scientific committee. Statistical advice was provided by Liz Barnes. JX drafted this manuscript based on the HREC approved protocol using the SPIRIT checklist.³⁵ This was edited and refined by SA and JK.

Funding As an unfunded study, there are no competing financial interests for the investigators.

Competing interests None declared.

Ethics approval This protocol and associated documentation has been approved by the SCHN Human Research Ethics Committee (HREC/15/SCHN/266) with respect to scientific content and compliance with applicable research and human subject regulations.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement The trial is registered on ClinicalTrials.gov and ANZCTR, both of which have open access. The participant information includes a flow sheet that summarises the study plan. The study findings will be presented in a report which will be submitted for publication in a relevant peer-reviewed journal to ensure dissemination to relevant healthcare professionals. Findings may also be submitted for presentation at local meetings or conferences. The final report will be made available to trial participants via the investigators. The participant-level data set may be made available for meta-analyses pending relevant HREC approval.

Open Access This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

REFERENCES

- Wilson BE, Cheney L, Patel B, *et al.* Appendectomy at a children's hospital: what has changed over a decade? *ANZ J Surg* 2012;82:639–43.
- McBurney C. Experience with early operative interference in cases of disease of the vermiform appendix by Charles McBurney, M.D., Visiting Surgeon to the Roosevelt Hospital, New York city. *Rev Surg* 1969;26:153–66.
- Esposito C, Calvo AI, Castagnetti M, *et al.* Open versus laparoscopic appendectomy in the pediatric population: a literature review and analysis of complications. *J Laparosc Adv Surg Tech A* 2012;22:834–9.
- Wray CJ, Kao LS, Millas SG, *et al.* Acute appendicitis: controversies in diagnosis and management. *Curr Probl Surg* 2013;50:54–86.
- Leung TTW, Dixon E, Gill M, *et al.* Bowel obstruction following appendectomy. *Ann Surg* 2009;250:51–3.
- Güller U, Rosella L, McCall J, *et al.* Negative appendectomy and perforation rates in patients undergoing laparoscopic surgery for suspected appendicitis. *Br J Surg* 2011;98:589–95.
- Flum DR, Morris A, Koepsell T, *et al.* Has misdiagnosis of appendicitis decreased over time? *JAMA* 2001;286:1748–53.
- St Peter SD, Aguayo P, Frase JD, *et al.* Initial laparoscopic appendectomy versus initial nonoperative management and interval appendectomy for perforated appendicitis with abscess: a prospective, randomized trial. *J Pediatr Surg* 2010;45:236–40.
- Lee SL, Islam S, Cassidy LD, *et al.* Antibiotics and appendicitis in the pediatric population: an American pediatric surgical association outcomes and clinical trials committee systematic review. *J Pediatr Surg* 2010;45:2181–5.
- Rollins KE, Varadhan KK, Neal KR, *et al.* Antibiotics versus appendectomy for the treatment of uncomplicated acute appendicitis: an updated meta-analysis of randomised controlled trials. *World J Surg* 2016;40:2305–18.
- Di Salomone S, Sibilio A, Giorgini E, *et al.* The NOTA study (non operative treatment for acute appendicitis): prospective study on the efficacy and safety of antibiotics (amoxicillin and clavulanic acid) for treating patients with right lower quadrant abdominal pain and long-term follow-up of conservatively treated suspected appendicitis. *Ann Surg* 2014;260:109–17.
- DiSaverio S, Birindelli A, Kelly MD, *et al.* WSUS Jerusalem guidelines for diagnosis and treatment of acute appendicitis. *World J Emerg Surg* 2016;11:34.
- Eriksson S, Granström L. Randomized controlled trial of appendectomy versus antibiotic therapy for acute appendicitis. *Br J Surg* 1995;82:166–9.
- Styrud J, Eriksson S, Nilsson I, *et al.* Appendectomy versus antibiotic treatment in acute appendicitis. A prospective multicentre randomized trial. *World J Surg* 2006;30:1033–7.

15. Varadhan KK, Neal KR, Lobo DN. Safety and efficacy of antibiotics compared with appendectomy for treatment of uncomplicated acute appendicitis: meta-analysis of randomised controlled trials. *BMJ* 2012;344:e2156.
16. Varadhan KK, Humes DJ, Neal KR, *et al.* Antibiotic therapy versus appendectomy for acute appendicitis: a meta-analysis. *World J Surg* 2009;34:199–209.
17. Liu K, Fogg L. Use of antibiotics alone for treatment of uncomplicated acute appendicitis: a systematic review and meta-analysis. *Surgery* 2011;150:673–83.
18. Sallinen V, Akl EA, You JJ, *et al.* Meta-analysis of antibiotics versus appendectomy for non-perforated acute appendicitis. *Br J Surg* 2016;103:656–67.
19. Salminen P, Paajanen H, Rautio T, *et al.* Antibiotic therapy vs appendectomy for treatment of uncomplicated acute appendicitis. *JAMA* 2015;313:2340–8.
20. Svensson JF, Patkova B, Almström M, *et al.* Nonoperative treatment with antibiotics versus surgery for acute nonperforated appendicitis in children. *Ann Surg* 2015;261:67–71.
21. Abeş M, Petik B, Kazil S. Nonoperative treatment of acute appendicitis in children. *J Pediatr Surg* 2007;42:1439–42.
22. Armstrong J, Merritt N, Jones S, *et al.* Non-operative management of early, acute appendicitis in children: Is it safe and effective? *J Pediatr Surg* 2014;49:782–5.
23. Koike Y, Uchida K, Matsushita K, *et al.* Intraluminal appendiceal fluid is a predictive factor for recurrent appendicitis after initial successful non-operative management of uncomplicated appendicitis in pediatric patients. *J Pediatr Surgery* 2014;49:1116–21.
24. Steiner Z, Buklan G, Stackievicz R, *et al.* A role for conservative antibiotic treatment in early appendicitis in children. *J Pediatr Surg* 2015;50:1566–8.
25. Gorter RR, van der Lee JH, Cense HA, *et al.* Initial antibiotic treatment for acute simple appendicitis in children is safe: short-term results from a multicenter, prospective cohort study. *Surgery* 2015;157:916–23.
26. Kaneko K, Tsuda M. Ultrasound-based decision making in the treatment of acute appendicitis in children. *J Pediatr Surg* 2004;39:1316–20.
27. Park HC, Kim BS, Lee BH. Efficacy of short-term antibiotic therapy for consecutive patients with mild appendicitis. *Am Surg* 2011;77:752–5.
28. Paudel G, Agrawal C, Regmi R, *et al.* Conservative treatment in acute appendicitis. *JNMA J Nepal Med Assoc* 2010;50:295–9.
29. Caruso AM, Pane A, Garau R, *et al.* Acute appendicitis in children: not only surgical treatment. *J Pediatr Surg* 2016;pii: S0022-3468:30277–9.
30. Hartwich J, Luks FI, Watson-Smith D, *et al.* Nonoperative treatment of acute appendicitis in children: a feasibility study. *J Pediatr Surg* 2016;51:111–16.
31. Minneci PC, Mahida JB, Lodwick DL, *et al.* Effectiveness of patient choice in nonoperative vs surgical management of pediatric uncomplicated acute appendicitis. *JAMA Surg* 2016;151:408.
32. Tanaka Y, Uchida H, Kawashima H, *et al.* Long-term outcomes of operative versus nonoperative treatment for uncomplicated appendicitis. *J Pediatr Surg* 2015;50:1893–7.
33. Scott IA. Non-inferiority trials: determining whether alternative treatments are good enough. *Med J Aust* 2009;190:326–30.
34. Harris PA, Taylor R, Thielke R, *et al.* Research electronic data capture (REDCap): metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009;42:377–81.
35. Chan A, Tetzlaff J, Gotzsche P, *et al.* SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013;346: e7586.