BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-013299
Article Type:	Protocol
Date Submitted by the Author:	05-Jul-2016
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Primary Subject Heading:	Surgery
Secondary Subject Heading:	Paediatrics
Keywords:	PAEDIATRIC SURGERY, Paediatric colorectal surgery < PAEDIATRIC SURGERY, Surgical pathology < PATHOLOGY, Paediatric pathology < PATHOLOGY

Acute Uncomplicated Appendicitis Study: Rationale and protocol for a multi-centre, prospective randomised controlled non-inferiority study to evaluate the safety and effectiveness of non-operative management in children with acute uncomplicated appendicitis

Short title: A Prospective Randomised Control Trial for Efficacy and Safety (APRES) of NOM for Appendicitis in Children

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Keywords:
Appendicitis, nonoperative management, paediatric surgery

Word count (abstract)/limit: 279/300 words
Word count (text)/limit: 3681 without reference list, figures and tables

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 multi-centre Australian study. The rationale and details of future analysis, in particular, non-inferiority calculations, cost effectiveness, feasibility and acceptability of each intervention.

Methods and Analysis

Design: A multicentre, prospective randomised controlled clinical trial, conducted in two 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 target recruitment is two hundred and twenty patients.
Interventions: Children in the control group will be treated with prophylactic antibiotics and appendicectomy, 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 Pearson X^2 test for categorical variables and independent sample T test or Mann-Whitney test for continuous variables. Non-inferiority for non-operative management will be tested using 1-sided Wald tests with an alpha 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, results will be reported through academic journals, seminars and conference presentations.

Registration:
ClinicalTrials.gov identifier: NCT02795793
ANZCTRN registration number: ACTRN12616000788471

STRENGTHS AND LIMITATIONS OF THIS STUDY:
Strengths

- One of the first, prospective 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.

Limitations

- Non-blinded;
- May include patients without appendicitis, the diagnosis is clinical and left to the treating physician.

INTRODUCTION

Appendicectomy 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 appendicectomies are for acute uncomplicated appendicitis (AUA). standard treatment of management has remained largely unchallenged since its introduction in the late nineteenth 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. The rate of short-term complications following appendicectomy, such as wound infection and ileus, has been reported to be between 1.9 to 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. In fact, children with appendicitis complicated by perforation, abscess or phlegmon formation are often preferentially treated primarily non-operatively with antibiotic therapy, with or without percutaneous drainage – a management for which there is an evidence base.[8, 9]

Systematic reviews and meta-analyses have demonstrated that antibiotics are a safe and effective treatment for AUA in adults.[10-13] The Appendicitis Acute (APPAC) multicentre, open-label, non-inferiority, randomised controlled trial in adults reported a significantly lower overall complication rate of 2.8% in the NOM group, compared to 20.5% in patients who received operative management. Importantly, only 7 of 256 patients in the non-operative group had progression to complicated appendicitis during the one year follow-up period.[14]

There is growing evidence that NOM is also safe and effective in children. Currently there has been one published randomised pilot study[15] and several cohort studies[16-27] 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 87.5-98.7%, a considerably shortened recovery time, and improved quality of life scores when compared to the operative management.[15-27] 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 randomised controlled trial 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 operative management (OM) in terms of safety and efficacy.

he 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, randomised controlled trial 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.[28]

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 approximately 92,000 emergency presentations, and approximately 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 (e.g. 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 (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. Total number of participant 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. Allocation ratio of 1:1 will be made via weighted minimisation using the following criteria: age (5 to 8 years or 9 to 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 commencement of treatment. Because of the nature of the interventions being evaluated, there will be no blinding in this study

Participant time line (Figure 1, Table 1)
Children allocated to OM may receive preoperative antibiotic prophylaxis as clinically indicated. Appendicectomy 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. 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) 100mg/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 (e.g. 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) 22.5mg/kg/dose twice per day to complete a total seven day course of antibiotics. Oral Ciprofloxacin 15mg/kg/dose twice daily and oral

Metronidazole 10mg/kg/dose twice daily 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 post-discharge, all participants will be seen in the outpatient clinic at 4 to 6 weeks after discharge as per standard practice, and a telephone interview will also be conducted at 1 week, 2 weeks, 3 months, 6 months and 12 months after discharge.

Table 1: Standard Care and Additional to Standard Care Procedures

Standard Care		
Procedure	**Timing**	**Dose, Frequency and/or Duration**
Appendicectomy 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 week after discharge	Once only

Additional to Standard Care		
Procedure	**Timing**	**Dose, Frequency and/or Duration**
Intravenous Piperacillin with Tazobactam	During admission	100mg/kg/dose every 8 hours for at least 24 hours up to 48 hours
Appendicectomy laparoscopic or open	During admission when patient failed to respond to antibiotic therapy	None, or once only
Oral Amoxicillin plus Clavulanic acid	Upon discharge	22.5 mg/kg/dose twice per day to complete a total 7-day course of antibiotics
Oral Ciprofloxacin and Metronidazole	Upon discharge for patient allergic to Augmentin	15 mg/kg/dose twice daily, and 10mg/kg/dose twice daily respectively to complete a total 7-day course of antibiotics
Telephone interview	1 week, 2 weeks, 3 months, 6 months and 12 months after discharge	5 to 10 minutes each interview. 5 times in total

OUTCOMES

Primary Outcome Measures

The primary outcome for the study is the treatment efficacy for both 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 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 is 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 months and 12 months post-randomisation.
2. Length of primary hospital stay from time of randomisation to discharge in hours.
3. Treatment-related complications.
4. Readmission and Emergency Department presentation within 12 months.
5. Cost of treatment in dollars – calculated at one year post randomisation. It will be based on fees registered in Medicare Benefits Schedule (MBS), Pharmaceutical Benefits Scheme (PBS) and institution standard pre-determined admission costing. It is calculated as a fee per day of in-hospital care, a fee for use of the operating room, 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.
6. Days before return to school from time of randomisation.
7. Days before return to normal activities from time of randomisation.

8. Total analgesia requirement (types, routes and mg/kg).
9. Antibiotic-associated side effects (e.g. rash, vomiting, diarrhoea or colitis).
10. Clinical outcomes of imaging-confirmed versus other suspected appendicitis in each group.

Sample size based on the reported post-appendicectomy complication rate of 1.9-8.8%[3, 4] and negative appendicectomy 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%[10, 14] in adults treated with NOM and 87.5-98.7% in children[15-27], we would expect a possible difference of treatment efficacy between control and treatment group to be between 15-25%. 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 approximately 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 approximately 300 cases of appendicitis each year (600 in total) of which approximately 60% will be uncomplicated, resulting in a total of 360 eligible cases. 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) 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 both intention-to-treat and per-protocol analyses will be performed. The intention-to-treat population will include all randomised participants who commence on a treatment, excluding consent withdrawals. The per-protocol population will include all participants who complete the study at 1year follow-up. A non-inferiority analysis will be performed to compare both the primary and secondary outcomes. Based on current adult literature, the treatment efficacy difference between operative and non-operative treatment is about 25-35%.[10-13] The most recent randomised controlled trial in adults used 25% as its non-inferiority margin.[14] In children, a 10% failure rate of NOM has been noted in the pilot study.[15] 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 X^2 test. Continuous variables will be characterised as means and standard deviations or medians and interquartile range 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 1-sided

Wald tests with an alpha level of 0.05. Statistical analyses will be performed using the SPSS Statistics Program.

The pre-determined power ($1 - \beta$) 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 (DMSB) will be convened for the study.

The DMSB 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 center;
- 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. One 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 DMSB 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 subject 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 DMSB 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.

Ethics and Dissemination

Research 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.

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 de-identified 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 old, 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 health care 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.

Authors contributions and declaration of interests

Dr Susan Adams and Dr Jonathan Karpelowsky initiated the project, and are the chief investigators. After a series of meetings and literature review, Dr Cyril Liu drafted the

protocol which was refined by Dr Susan Adams and Dr Jonathan Karpelowsky with input from the SCHN HREC scientific committee. Statistical advice was provided by Liz Barnes. Jane Xu drafted this manuscript based on the HREC approved protocol using the SPIRIT checklist.[29] This was edited and refined by Dr Susan Adams and Dr Jonathan Karpelowsky.

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

Competing interests statement
None to declare

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 randomised controlled trials 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.

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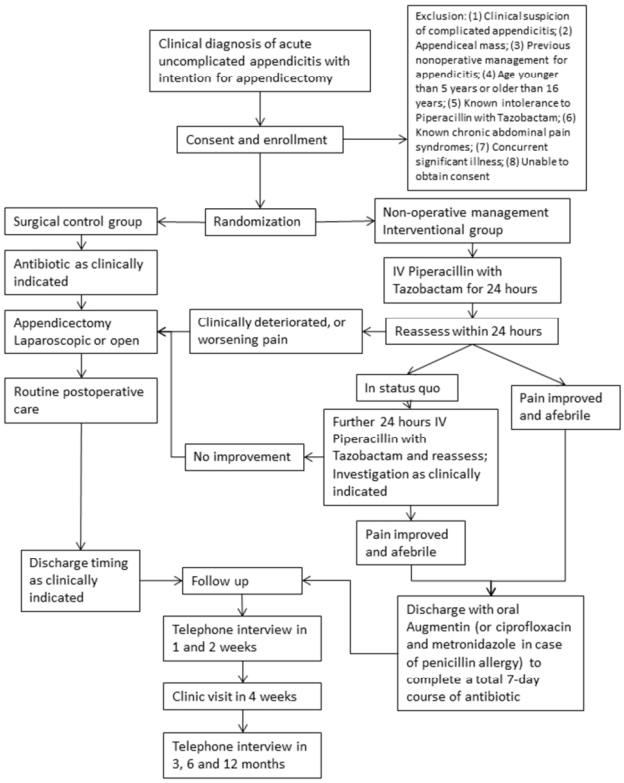


Figure 1 Study Design Diagram and Participant Timeline
Figure 1
209x297mm (150 x 150 DPI)

Appendix 1: Sample Study Information Sheet and Informed Consent form

PARENT INFORMATION SHEET

A Prospective Randomized Controlled Non-inferiority Study to Evaluate the Safety and Effectiveness of Non-operative Management in Children with Acute Uncomplicated Appendicitis

Investigators:

Jonathan Karpelowsky	Department of Paediatric Surgery, Children's Hospital at Westmead, 9845 3235
Soundappan Soundappan	Department of Paediatric Surgery, Children's Hospital at Westmead, 9845 3235
Dermot McDowell	Department of Paediatric Surgery, Children's Hospital at Westmead, 9845 3235
Susan Adams	Department of Paediatric Surgery, Sydney Children's Hospital, Randwick. 9382 1776
Yingrui Liu	Department of Paediatric Surgery, Sydney Children's Hospital, Randwick. 9382 0000

Introduction

We would like you to consider taking part in a research study that will be conducted in The Department of Paediatric Surgery, Sydney Children's Hospital Network, Randwick and Westmead campuses.

This Participant Information Sheet/Consent Form tells you about the research project. It explains the two treatments being compared and the research involved. Knowing what is involved will help you decide if you want your child to take part in the research.

Please read this information carefully. Please ask your study doctor if there is anything you do not understand or if you would like more information. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or local doctor.

Participation in this research is voluntary. If you do not wish for your child to take part, they do not have to. Your child will receive the best possible care whether or not he/she takes part in the study.

What is Acute Appendicitis?

Appendicitis is an infection of a small blind ending tubular structure (the appendix) that arises from the large bowel. In the earlier stages this infection it is confined to the appendix. This is termed *uncomplicated appendicitis*. If the infection is not treated then it may progress to rupture of the appendix resulting in an abscess, or pus within the abdominal cavity. This is termed *complicated appendicitis.*

What is the study about?

For almost 100 years the accepted treatment of appendicitis has been an operation to remove the appendix. This treatment was developed when no other alternatives were available and predated the development of highly effective antibiotics in use today. We now know from studies in adults and some reports in children, that uncomplicated appendicitis can be successfully treated without the need for an operation. In fact even in *complicated appendicitis*, many surgeons will opt to treat the infection with antibiotics rather than an operation, and this has become a common approach.

Your child is invited to take part in this research project. This study aims to assess if clinically uncomplicated acute appendicitis can be effectively and safely managed without the need for an operation. This will be done by comparing outcomes for children with uncomplicated appendicitis treated with antibiotics alone with those who are treated with an operation. Participants will be assigned randomly to be treated with either antibiotics alone or with appendicectomy.

Who can participate in the study?

Children from age 5-16 with a diagnosis of uncomplicated acute appendicitis will be invited to participate.

What will the study involve? Or what kind of medications will my child receive?

Upon admission to hospital your doctor will decide if your child has appendicitis. At that point you will be invited to take part in this study.

If you decide to take part, your child will be allocated randomly to one of two “arms” or groups of the study.

GROUP 1 Antibiotics alone -Intravenous Tazocin (a type of antibiotic) followed by oral antibiotics
GROUP 2 Appendicectomy

For Group 1, your child will require an IV cannula and be treated with intravenous antibiotics for up to 48 hours. They will be closely monitored. If at any time their condition worsens or if the antibiotic treatment is not successful, they will have their appendix removed as per group 2 (see below). . Blood tests, x-rays and ultrasounds will only be done if the doctor thinks they are required in order to make the diagnosis or monitor treatment as part of routine clinical care. There are no extra investigations or blood tests that are required as part of this study. Pain relief will be provided. Once your child is comfortable, eating and drinking and signs of infection have abated, they will be discharged home on oral antibiotics for a total antibiotic course of 7 days. Following discharge we will telephone you at 1 week and 2

weeks and see you in the clinic at 4 weeks. We will make further contact at 3, 6 and 12 months by telephone to see how your child is. Each telephone conversation should take no more than 10 minutes.

For Group 2, your child will be admitted, have an IV cannula as part of routine care and taken to theatre to have their appendix removed. The operation will be explained by the surgical team and your informed consent for the procedure will be obtained as part of standard care in preparation for theatre. A single dose of antibiotics will be given at the time of the operation as is usual practice. Antibiotics may be continued only if thought necessary for your child's care by the treating surgeon after the operation. Post-operatively, your child will be closely monitored. Pain relief will be provided. Blood tests, x-rays and ultrasounds will only be done if the doctor thinks they are required in order to make the diagnosis or monitor treatment as part of routine clinical care. There are no extra investigations or blood tests that are required as part of this study. Once your child is eating and drinking and signs of infection have abated, they will be discharged home.

Following discharge we will telephone you at 1 week and 2 weeks and see your child in the clinic at 4 weeks. We will make further contact at 3, 6 and 12 months by telephone to see how your child is. Each telephone conversation should take no more than 10 minutes.

As part of routine clinical care, your child will be seen by the routine treating doctors every day.

The attached flow diagram explains the decision making processes during the study

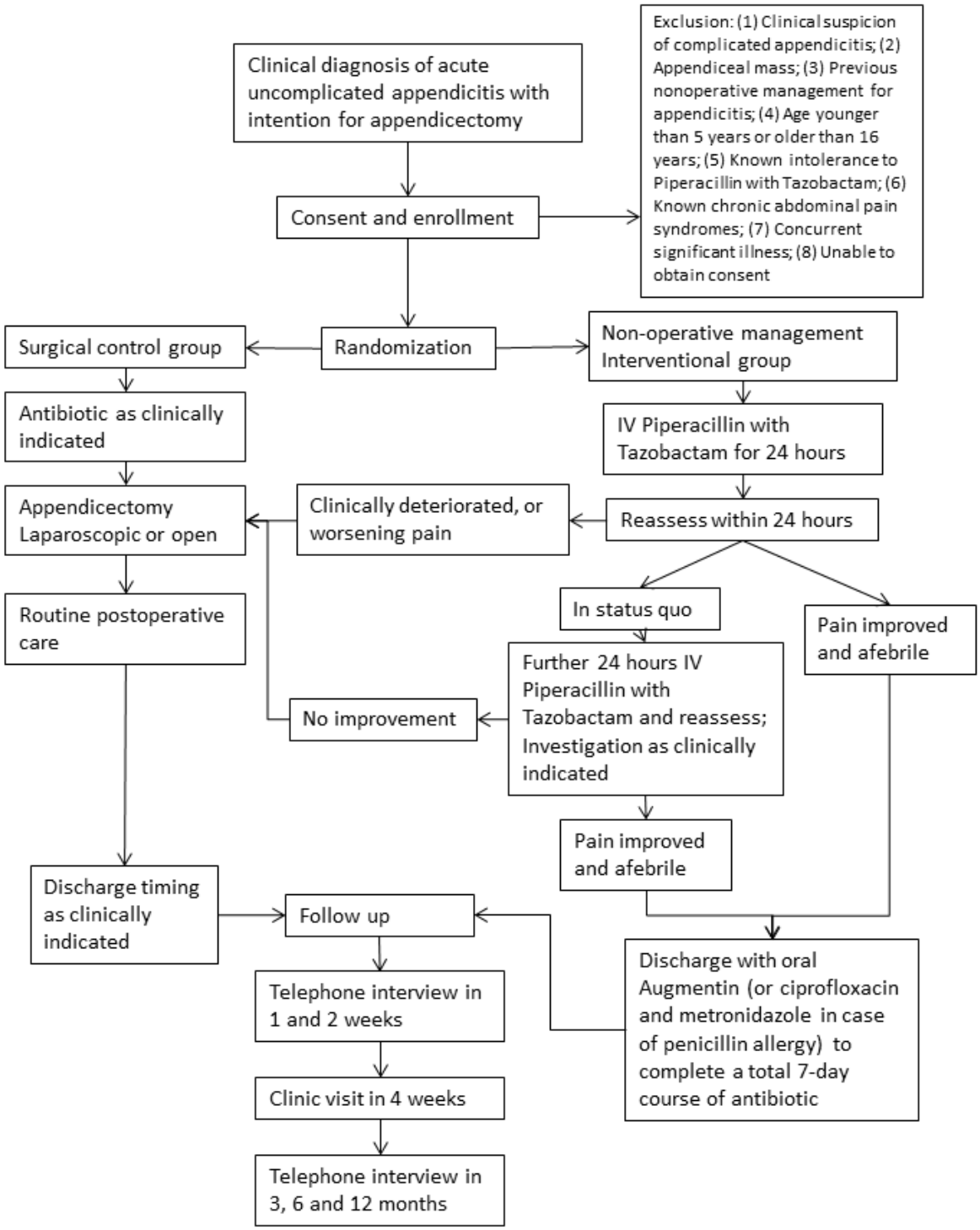
Information collected during the study period would include:
Data of birth
Age at presentation
Allergies
Weight
Past medical history
Symptoms and their duration
Physical examination findings
Results of any investigations
Result of randomisation

Group 1
- Antibiotic dose and duration
- Temperature pulse and blood pressure observations as well as pain assessment
- Results of any tests done as part of routine clinical care
- Other medications required including pain killers
- Whether the child proceeded to have their appendix removed
- Dietary intake
- Duration of hospitalisation
- Progress at 1 week, 2 weeks, 4 weeks, 3 months, 6 months and 12 months

Group 2
- Operative findings
- Dose and duration of any antibiotics
- Temperature pulse and blood pressure observations as well, as pain assessment

- Results of any tests done as part of routine clinical care
- Other medications required including pain killers
- Any complications
- Dietary intake
- Duration of hospitalisation
- Progress at 1 week, 2 weeks, 4 weeks, 3 months, 6 months and 12 months

FLOW DIAGRAM EXPLAINING THE STUDY



Are there any benefits for my child participating in the study?

Depending on the randomisation process, your child may avoid having an operation for their appendicitis. The potential advantage of this is a faster recovery, less pain and no complications from having an operation or anaesthetic.
We hope that the results from this study will help confirm that children with uncomplicated appendicitis can be safely managed without the need for an operation.
.

Are there any side-effects and risk associated with this study?

In prior studies up to 10% of children who initially have antibiotic treatment, subsequently need to have their appendix removed. This is usually clear during the first 24 -48 hours and almost always by 30 days. There is no evidence that children who are treated initially without an operation, have an increased risk of complicated appendicitis should the antibiotic treatment not work.

What will happen to information collected about your child's treatment?

This study will involve the collection and processing of treatment data. By signing the consent form you consent to the study doctor and relevant research staff collecting and using personal information about your child for the research project. Any information obtained in connection with this research project that can identify you/your child will remain confidential. Your child's information will only be used for the purpose of this research project and will only be disclosed with your permission. Information about your child may be obtained from his/her health records held at this and other health services for the purpose of this research. By signing the consent form you also agree to the research team accessing health records if they are relevant to your child's participation in this research project. We will also keep your child's files in locked storage areas, and use password-protected computer files. All paper copies of data collected will be stored for a minimum of 15 years - or for those under 18 years of age; it will be stored for 7 years after the date of their 18th birthday

What happens if I choose to withdraw from this study?

Participation in this project is voluntary and if you decide not to take part or decide to withdraw at any time this will not otherwise affect your child's care at the Hospital. Data collected on your child will not be stored or utilised for analysis.

If you have any questions about the conduct of this study, please do not hesitate to discuss them with

Jonathan Karpelowsky	Department of Paediatric Surgery, Children's Hospital at Westmead, 9845 3235
Soundappan Soundappan	Department of Paediatric Surgery, Children's Hospital at Westmead, 9845 3235
Dermot McDowell	Department of Paediatric Surgery, Children's Hospital at Westmead, 9845 3235
Susan Adams	Department of Paediatric Surgery, Sydney Children's Hospital, Randwick. 9382 1776
Yingrui Liu	Department of Paediatric Surgery, Sydney Children's Hospital, Randwick. 9382 0000

This project has been approved by the Sydney Children's Hospitals Network Human Research Ethics Committee. If you have any concerns about the conduct of this study, please do not hesitate to contact the Executive Officer of the Ethics Committee (02 9845 3066) and quote approval number HREC/15/SCHN/266.

This Information Sheet is for you to keep. We will also give you a copy of the signed consent form.

Parent Consent Form

A Prospective Randomized Controlled Study to Evaluate the Safety and Effectiveness of Non-operative Management in Children with Acute Uncomplicated Appendicitis

Investigators:

Jonathan Karpelowsky	Department of Paediatric Surgery, Children's Hospital at Westmead, 9845 3235
Soundappan Soundappan	Department of Paediatric Surgery, Children's Hospital at Westmead, 9845 3235
Dermot McDowell	Department of Paediatric Surgery, Children's Hospital at Westmead, 9845 3235
Susan Adams	Department of Paediatric Surgery, Sydney Children's Hospital, Randwick. 9382 1776
Yingrui Liu	Department of Paediatric Surgery, Sydney Children's Hospital, Randwick. 9382 0000

Declaration by Parent

I have read the Participant Information Sheet or someone has read it to me in a language that I understand.

I understand the purposes, procedures and risks of the research described in the project.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to my child participating in this research project as described and understand that I am free to withdraw them at any time during the project without affecting their future health care.

I understand that I will be given a signed copy of this document to keep.

I give permission for the child's doctors, other health professionals, hospitals or laboratories outside this hospital to release information to Sydney Children's Hospital Network concerning my child's condition and treatment for the purposes of this project. I understand that such information will remain confidential.

NAME OF PARENT: _____ (Please print)

SIGNATURE OF PARENT: _____ Date: _____

NAME OF PERSON WHO OBTAINED CONSENT: _____ (Please print)

SIGNATURE OF PERSON WHO OBTAINED CONSENT: _____ Date: _____

Declaration by Study Doctor

I have given a verbal explanation of the research project, its procedures and risks and I believe that the parent/guardian of the participant has understood that explanation.

NAME OF STUDY DOCTOR: _____
(Please print)

SIGNATURE OF STUDY DOCTOR: _____ Date: _____

BMJ Open

Acute Uncomplicated Appendicitis Study: Rationale and protocol for a multi-centre, prospective randomised controlled non-inferiority study to evaluate the safety and effectiveness of non-operative management in children with acute uncomplicated appendicitis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-013299.R1
Article Type:	Protocol
Date Submitted by the Author:	05-Oct-2016
Complete List of Authors:	Xu, Jane; The University of New South Wales Liu, Yingrui; Sydney Children\'s Hospital Randwick, Paediatric Surgery Adams, Susan; Sydney Children\'s Hospital Randwick, Paediatric Surgery; The University of New South Wales Karpelowsky, Jonathan ; The Children's Hospital at Westmead, Paediatric Surgery; University of Sydney
Primary Subject Heading:	Surgery
Secondary Subject Heading:	Paediatrics
Keywords:	PAEDIATRIC SURGERY, Paediatric colorectal surgery < PAEDIATRIC SURGERY, Surgical pathology < PATHOLOGY, Paediatric pathology < PATHOLOGY

Acute Uncomplicated Appendicitis Study: Rationale and protocol for a multi-centre, prospective randomised controlled non-inferiority study to evaluate the safety and effectiveness of non-operative management in children with acute uncomplicated appendicitis

Short title: A Prospective Randomised Control Trial for Efficacy and Safety (APRES) of NOM for Appendicitis in Children

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Keywords:
Appendicitis, nonoperative management, paediatric surgery

Word count (abstract)/limit: 284/300 words
Word count (text)/limit: 3674 without reference list, figures and tables

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 multi-centre Australian study. The rationale and details of future analysis, in particular, non-inferiority calculations, cost effectiveness, feasibility and acceptability of each intervention.

Methods and Analysis

Design: A multicentre, prospective randomised controlled clinical trial, conducted in two 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 two hundred and twenty patients.
Interventions: Children in the control group will be treated with prophylactic antibiotics and appendicectomy, 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 Pearson X^2 test for categorical variables and independent sample T test or Mann-Whitney test for continuous variables. Non-inferiority for non-operative management will be tested using 1-sided Wald tests with an alpha 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, results will be reported through academic journals, seminars and conference presentations.

Registration:
ClinicalTrials.gov identifier: NCT02795793
ANZCTRN registration number: ACTRN12616000788471

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.

Limitations

- Non-blinded;
- May include patients without appendicitis, the diagnosis is clinical and left to the treating physician.

INTRODUCTION

Appendicectomy 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 appendicectomies are for acute uncomplicated appendicitis (AUA). Standard treatment of management has remained largely unchallenged since its introduction in the late nineteenth 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, has been reported to be between 1.9 to 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 in adults reported a significantly lower overall complication rate of 2.8% in the NOM group, compared to 20.5% in patients who received operative management. Importantly, only 7 of 256 patients in the non-operative group had progression to complicated appendicitis during the one 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 study[20] 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 to the operative management.[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 randomised controlled trial 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 operative management (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, randomised controlled trial 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 approximately 92,000 emergency presentations, and approximately 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 (e.g. 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 (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. Total number of participant 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. Allocation ratio of 1:1 will be made via weighted minimisation using the following criteria: age (5 to 8 years or 9 to 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 commencement of treatment. Because of the nature of the interventions being evaluated, there will be no blinding in this study

Participant time line (Figure 1, Table 1)
Children allocated to OM may receive preoperative antibiotic prophylaxis as clinically indicated. Appendicectomy 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. 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) 100mg/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 (e.g. 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) 22.5mg/kg/dose twice per day to complete a total seven day course of antibiotics. Oral Ciprofloxacin 15mg/kg/dose twice daily and oral

Metronidazole 10mg/kg/dose twice daily 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 post-discharge, all participants will be seen in the outpatient clinic at 4 to 6 weeks after discharge as per standard practice, and a telephone interview will also be conducted at 1 week, 2 weeks, 3 months, 6 months and 12 months after discharge.

Table 1: Standard Care and Additional to Standard Care Procedures

Standard Care		
Procedure	**Timing**	**Dose, Frequency and/or Duration**
Appendicectomy 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 week after discharge	Once only

Additional to Standard Care		
Procedure	**Timing**	**Dose, Frequency and/or Duration**
Intravenous Piperacillin with Tazobactam	During admission	100mg/kg/dose every 8 hours for at least 24 hours up to 48 hours
Appendicectomy laparoscopic or open	During admission when patient failed to respond to antibiotic therapy	None, or once only
Oral Amoxicillin plus Clavulanic acid	Upon discharge	22.5 mg/kg/dose twice per day to complete a total 7-day course of antibiotics
Oral Ciprofloxacin and Metronidazole	Upon discharge for patient allergic to Augmentin	15 mg/kg/dose twice daily, and 10mg/kg/dose twice daily respectively to complete a total 7-day course of antibiotics
Telephone interview	1 week, 2 weeks, 3 months, 6 months and 12 months after discharge	5 to 10 minutes each interview. 5 times in total

OUTCOMES

Primary Outcome Measures

The primary outcome for the study is the treatment efficacy for both 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 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 is 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 months and 12 months post-randomisation.
2. Length of primary hospital stay from time of randomisation to discharge in hours.
3. Treatment-related complications.
4. Readmission and Emergency Department presentation within 12 months.
5. Cost of treatment in dollars – calculated at one year post randomisation. It will be based on fees registered in Medicare Benefits Schedule (MBS), Pharmaceutical Benefits Scheme (PBS) and institution standard pre-determined admission costing. It is calculated as a fee per day of in-hospital care, a fee for use of the operating room, 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.
6. Days before return to school from time of randomisation.
7. Days before return to normal activities from time of randomisation.

8. Total analgesia requirement (types, routes and mg/kg).
9. Antibiotic-associated side effects (e.g. rash, vomiting, diarrhoea or colitis).
10. Clinical outcomes of imaging-confirmed versus other suspected appendicitis in each group.

Sample size based on the reported post-appendicectomy complication rate of 1.9-8.8%[3, 4] and negative appendicectomy 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 control and treatment group to be between 15-25%. 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 approximately 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 approximately 300 cases of appendicitis each year (600 in total) of which approximately 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 both intention-to-treat and per-protocol analyses will be performed. The intention-to-treat population will include all randomised participants who commence 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 both 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 randomised controlled trial 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 X^2 test. Continuous variables will be characterised as means and standard deviations or medians and interquartile range 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 1-sided Wald tests with an alpha level of 0.05. Statistical analyses will be performed using the SPSS Statistics Program.

The pre-determined power $(1 - \beta)$ 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 (DMSB) will be convened for the study.

The DMSB 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. One 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 DMSB 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 subject 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 DMSB 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.

Ethics and Dissemination

Research 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.

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 de-identified 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 old, 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 health care 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.

Authors contributions and declaration of interests

Dr Susan Adams and Dr Jonathan Karpelowsky initiated the project, and are the chief investigators. After a series of meetings and literature review, Dr Cyril Liu drafted the protocol which was refined by Dr Susan Adams and Dr Jonathan Karpelowsky with input from the SCHN HREC scientific committee. Statistical advice was provided by Liz Barnes. Jane Xu drafted this manuscript based on the HREC approved protocol using the SPIRIT checklist.[35] This was edited and refined by Dr Susan Adams and Dr Jonathan Karpelowsky.

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

Competing interests statement
None to declare

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 randomised controlled trials 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.

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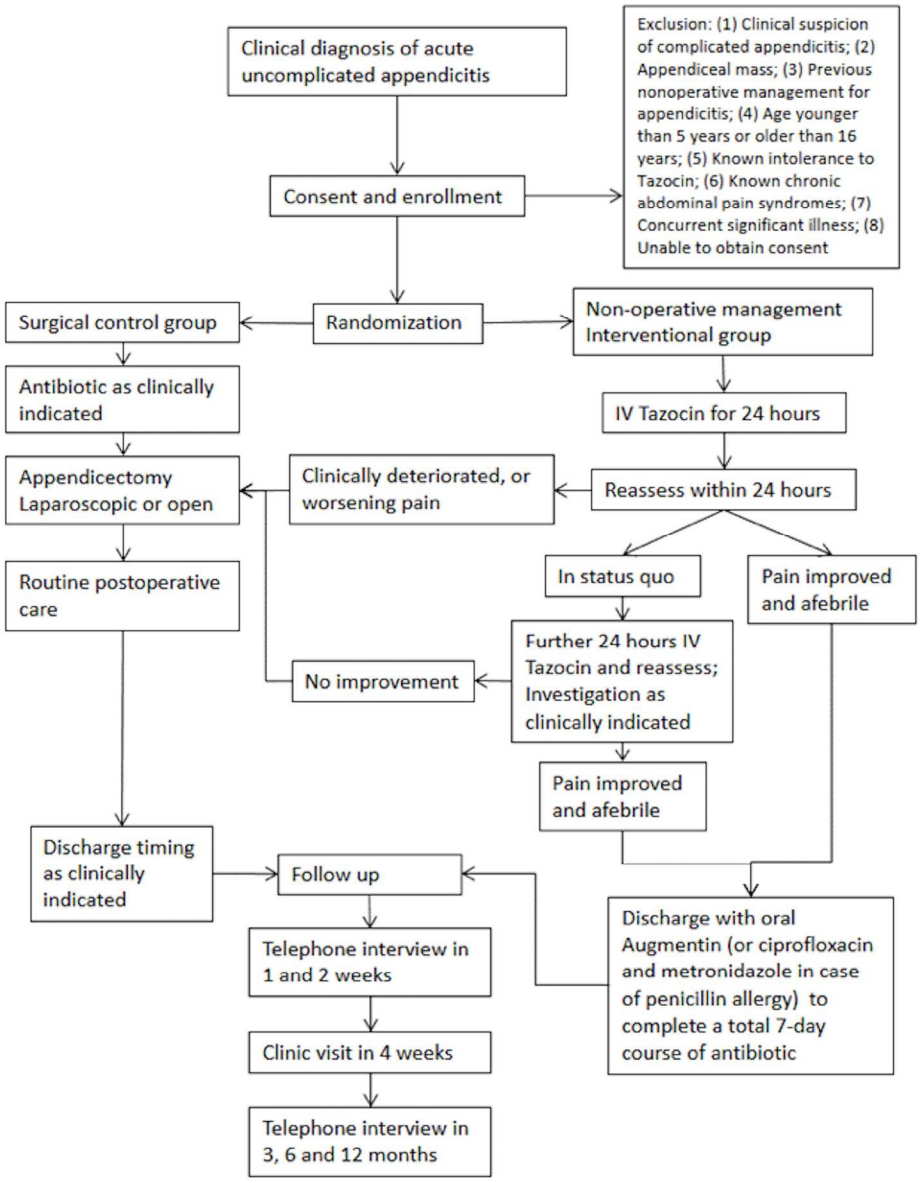


Figure 1 Study Design Diagram and Participant Timeline
Figure 1
220x284mm (300 x 300 DPI)

Appendix 1: Sample Study Information Sheet and Informed Consent form

PARENT INFORMATION SHEET

A Prospective Randomized Controlled Non-inferiority Study to Evaluate the Safety and Effectiveness of Non-operative Management in Children with Acute Uncomplicated Appendicitis

Investigators:

Jonathan Karpelowsky	Department of Paediatric Surgery, Children's Hospital at Westmead, 9845 3235
Soundappan Soundappan	Department of Paediatric Surgery, Children's Hospital at Westmead, 9845 3235
Dermot McDowell	Department of Paediatric Surgery, Children's Hospital at Westmead, 9845 3235
Susan Adams	Department of Paediatric Surgery, Sydney Children's Hospital, Randwick. 9382 1776
Yingrui Liu	Department of Paediatric Surgery, Sydney Children's Hospital, Randwick. 9382 0000

Introduction

We would like you to consider taking part in a research study that will be conducted in The Department of Paediatric Surgery, Sydney Children's Hospital Network, Randwick and Westmead campuses.

This Participant Information Sheet/Consent Form tells you about the research project. It explains the two treatments being compared and the research involved. Knowing what is involved will help you decide if you want your child to take part in the research.

Please read this information carefully. Please ask your study doctor if there is anything you do not understand or if you would like more information. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or local doctor.

Participation in this research is voluntary. If you do not wish for your child to take part, they do not have to. Your child will receive the best possible care whether or not he/she takes part in the study.

What is Acute Appendicitis?

Appendicitis is an infection of a small blind ending tubular structure (the appendix) that arises from the large bowel. In the earlier stages this infection it is confined to the appendix. This is termed *uncomplicated appendicitis*. If the infection is not treated then it may progress to rupture of the appendix resulting in an abscess, or pus within the abdominal cavity. This is termed *complicated appendicitis.*

What is the study about?

For almost 100 years the accepted treatment of appendicitis has been an operation to remove the appendix. This treatment was developed when no other alternatives were available and predated the development of highly effective antibiotics in use today. We now know from studies in adults and some reports in children, that uncomplicated appendicitis can be successfully treated without the need for an operation. In fact even in *complicated appendicitis*, many surgeons will opt to treat the infection with antibiotics rather than an operation, and this has become a common approach.

Your child is invited to take part in this research project. This study aims to assess if clinically uncomplicated acute appendicitis can be effectively and safely managed without the need for an operation. This will be done by comparing outcomes for children with uncomplicated appendicitis treated with antibiotics alone with those who are treated with an operation. Participants will be assigned randomly to be treated with either antibiotics alone or with appendicectomy.

Who can participate in the study?

Children from age 5-16 with a diagnosis of uncomplicated acute appendicitis will be invited to participate.

What will the study involve? Or what kind of medications will my child receive?

Upon admission to hospital your doctor will decide if your child has appendicitis. At that point you will be invited to take part in this study.

If you decide to take part, your child will be allocated randomly to one of two “arms” or groups of the study.

GROUP 1 Antibiotics alone -Intravenous Tazocin (a type of antibiotic) followed by oral antibiotics
GROUP 2 Appendicectomy

For Group 1, your child will require an IV cannula and be treated with intravenous antibiotics for up to 48 hours. They will be closely monitored. If at any time their condition worsens or if the antibiotic treatment is not successful, they will have their appendix removed as per group 2 (see below). . Blood tests, x-rays and ultrasounds will only be done if the doctor thinks they are required in order to make the diagnosis or monitor treatment as part of routine clinical care. There are no extra investigations or blood tests that are required as part of this study. Pain relief will be provided. Once your child is comfortable, eating and drinking and signs of infection have abated, they will be discharged home on oral antibiotics for a total antibiotic course of 7 days. Following discharge we will telephone you at 1 week and 2

weeks and see you in the clinic at 4 weeks. We will make further contact at 3, 6 and 12 months by telephone to see how your child is. Each telephone conversation should take no more than 10 minutes.

For Group 2, your child will be admitted, have an IV cannula as part of routine care and taken to theatre to have their appendix removed. The operation will be explained by the surgical team and your informed consent for the procedure will be obtained as part of standard care in preparation for theatre. A single dose of antibiotics will be given at the time of the operation as is usual practice. Antibiotics may be continued only if thought necessary for your child's care by the treating surgeon after the operation. Post-operatively, your child will be closely monitored. Pain relief will be provided. Blood tests, x-rays and ultrasounds will only be done if the doctor thinks they are required in order to make the diagnosis or monitor treatment as part of routine clinical care. There are no extra investigations or blood tests that are required as part of this study. Once your child is eating and drinking and signs of infection have abated, they will be discharged home.

Following discharge we will telephone you at 1 week and 2 weeks and see your child in the clinic at 4 weeks. We will make further contact at 3, 6 and 12 months by telephone to see how your child is. Each telephone conversation should take no more than 10 minutes.

As part of routine clinical care, your child will be seen by the routine treating doctors every day.

The attached flow diagram explains the decision making processes during the study

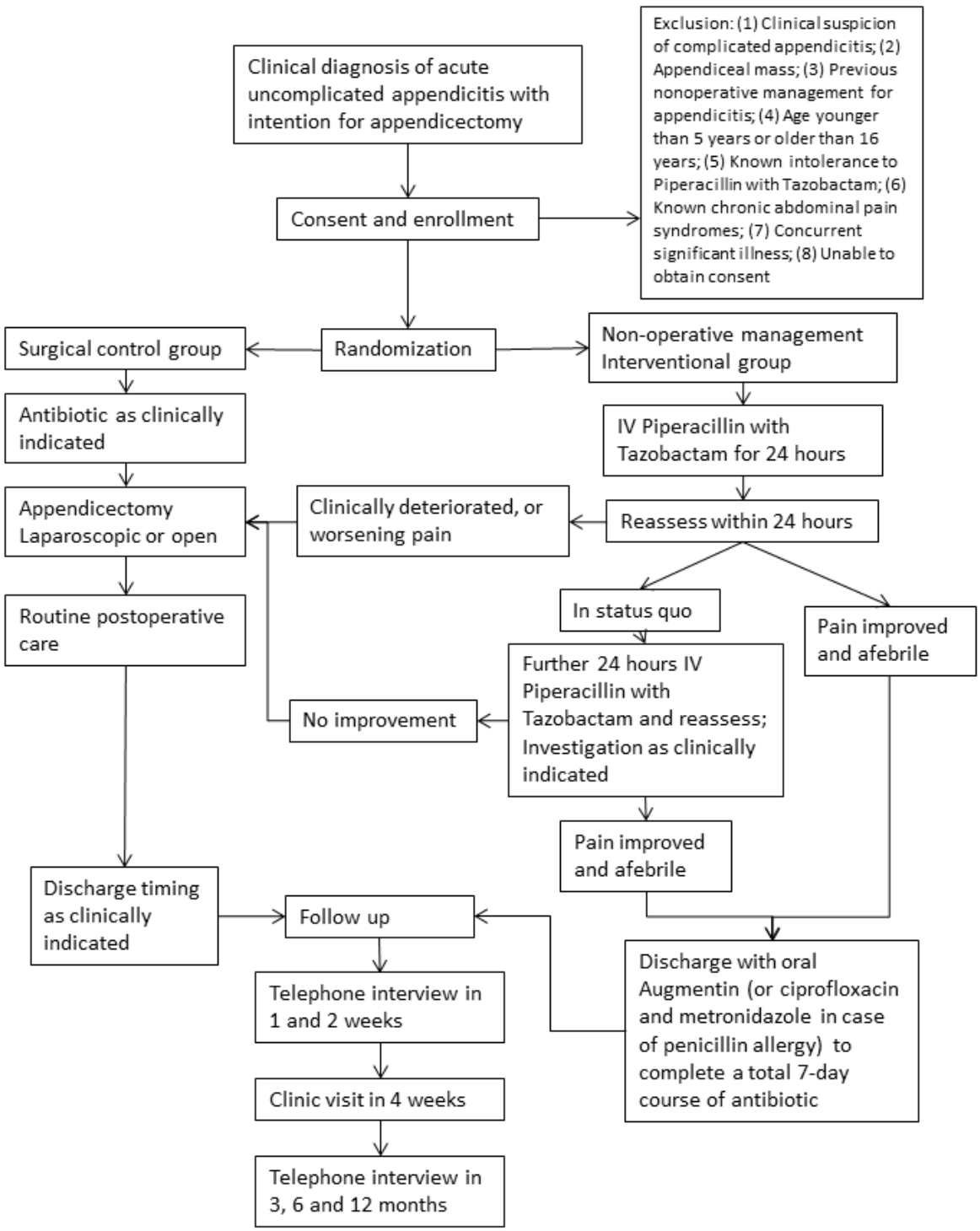
Information collected during the study period would include:
Data of birth
Age at presentation
Allergies
Weight
Past medical history
Symptoms and their duration
Physical examination findings
Results of any investigations
Result of randomisation

Group 1
- Antibiotic dose and duration
- Temperature pulse and blood pressure observations as well as pain assessment
- Results of any tests done as part of routine clinical care
- Other medications required including pain killers
- Whether the child proceeded to have their appendix removed
- Dietary intake
- Duration of hospitalisation
- Progress at 1 week, 2 weeks, 4 weeks, 3 months, 6 months and 12 months

Group 2
- Operative findings
- Dose and duration of any antibiotics
- Temperature pulse and blood pressure observations as well, as pain assessment

- Results of any tests done as part of routine clinical care
- Other medications required including pain killers
- Any complications
- Dietary intake
- Duration of hospitalisation
- Progress at 1 week, 2 weeks, 4 weeks, 3 months, 6 months and 12 months

FLOW DIAGRAM EXPLAINING THE STUDY



Are there any benefits for my child participating in the study?

Depending on the randomisation process, your child may avoid having an operation for their appendicitis. The potential advantage of this is a faster recovery, less pain and no complications from having an operation or anaesthetic.
We hope that the results from this study will help confirm that children with uncomplicated appendicitis can be safely managed without the need for an operation.
.

Are there any side-effects and risk associated with this study?

In prior studies up to 10% of children who initially have antibiotic treatment, subsequently need to have their appendix removed. This is usually clear during the first 24 -48 hours and almost always by 30 days. There is no evidence that children who are treated initially without an operation, have an increased risk of complicated appendicitis should the antibiotic treatment not work.

What will happen to information collected about your child's treatment?

This study will involve the collection and processing of treatment data. By signing the consent form you consent to the study doctor and relevant research staff collecting and using personal information about your child for the research project. Any information obtained in connection with this research project that can identify you/your child will remain confidential. Your child's information will only be used for the purpose of this research project and will only be disclosed with your permission. Information about your child may be obtained from his/her health records held at this and other health services for the purpose of this research. By signing the consent form you also agree to the research team accessing health records if they are relevant to your child's participation in this research project. We will also keep your child's files in locked storage areas, and use password-protected computer files. All paper copies of data collected will be stored for a minimum of 15 years - or for those under 18 years of age; it will be stored for 7 years after the date of their 18th birthday

What happens if I choose to withdraw from this study?

Participation in this project is voluntary and if you decide not to take part or decide to withdraw at any time this will not otherwise affect your child's care at the Hospital. Data collected on your child will not be stored or utilised for analysis.

If you have any questions about the conduct of this study, please do not hesitate to discuss them with

Jonathan Karpelowsky	Department of Paediatric Surgery, Children's Hospital at Westmead, 9845 3235
Soundappan Soundappan	Department of Paediatric Surgery, Children's Hospital at Westmead, 9845 3235
Dermot McDowell	Department of Paediatric Surgery, Children's Hospital at Westmead, 9845 3235
Susan Adams	Department of Paediatric Surgery, Sydney Children's Hospital, Randwick. 9382 1776
Yingrui Liu	Department of Paediatric Surgery, Sydney Children's Hospital, Randwick. 9382 0000

This project has been approved by the Sydney Children's Hospitals Network Human Research Ethics Committee. If you have any concerns about the conduct of this study, please do not hesitate to contact the Executive Officer of the Ethics Committee (02 9845 3066) and quote approval number HREC/15/SCHN/266.

This Information Sheet is for you to keep. We will also give you a copy of the signed consent form.

Parent Consent Form

A Prospective Randomized Controlled Study to Evaluate the Safety and Effectiveness of Non-operative Management in Children with Acute Uncomplicated Appendicitis

Investigators:

Jonathan Karpelowsky	Department of Paediatric Surgery, Children's Hospital at Westmead, 9845 3235
Soundappan Soundappan	Department of Paediatric Surgery, Children's Hospital at Westmead, 9845 3235
Dermot McDowell	Department of Paediatric Surgery, Children's Hospital at Westmead, 9845 3235
Susan Adams	Department of Paediatric Surgery, Sydney Children's Hospital, Randwick. 9382 1776
Yingrui Liu	Department of Paediatric Surgery, Sydney Children's Hospital, Randwick. 9382 0000

Declaration by Parent

I have read the Participant Information Sheet or someone has read it to me in a language that I understand.

I understand the purposes, procedures and risks of the research described in the project.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to my child participating in this research project as described and understand that I am free to withdraw them at any time during the project without affecting their future health care.

I understand that I will be given a signed copy of this document to keep.

I give permission for the child's doctors, other health professionals, hospitals or laboratories outside this hospital to release information to Sydney Children's Hospital Network concerning my child's condition and treatment for the purposes of this project. I understand that such information will remain confidential.

NAME OF PARENT: _____ (Please print)

SIGNATURE OF PARENT: _____ Date: _____

NAME OF PERSON WHO OBTAINED CONSENT: _____ (Please print)

SIGNATURE OF PERSON WHO OBTAINED CONSENT: _____ Date: _____

Declaration by Study Doctor

I have given a verbal explanation of the research project, its procedures and risks and I believe that the parent/guardian of the participant has understood that explanation.

NAME OF STUDY DOCTOR: _____
(Please print)

SIGNATURE OF STUDY DOCTOR: _____ Date: _____