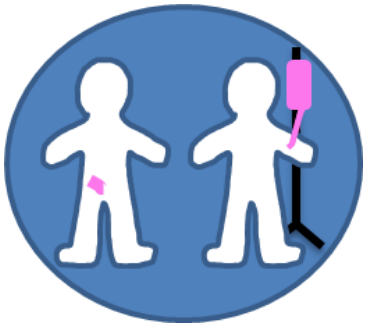
CONTRACT



CONservative TREatment of Appendicitis in Children – a randomised controlled Trial – CONTRACT (Feasibility study)

University Hospital Southampton NHS
NHS Foundation Trust

Version 2, 10-April-2017

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FUNDER

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Protocol Information

This protocol describes the CONTRACT study and provides information about procedures for entering participants. The protocol should not be used as a guide for the treatment of other non- study participants; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study, but sites entering participants for the first time are advised to contact Southampton Clinical Trials Unit to confirm they have the most recent version.

Compliance

This study will adhere to the principles of Good Clinical Practice (GCP). It will be conducted in compliance with the protocol, the Data Protection Act and all other regulatory requirements, as appropriate.

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LIST OF ABBREVIATIONS

AE	Adverse Event
A&E	Accident and Emergency department
CHU-9D	Child Health Utility 9D
COS	Core Outcome Set
eCRF	Electronic Case Report Form
CRF	Clinical Research Facility
CRP	C Reactive Protein
CRN	Clinical Research Network
CSRI	Client Service Receipt Inventory
CTCAE	Common Terminology Criteria for Adverse Events
DMSC	Data Monitoring and Safety Committee
GCP	Good Clinical Practice
HE	Health Economics
ISF	Investigator Site File
IV	Intravenous
MHRA	Medicines and Healthcare products Regulatory Agency
NBM	Nil by mouth
NIHR	National Institute of Health Research
PICU	Paediatric Intensive Care Unit
PPI	Patient and Public Involvement
RCT	Randomised Clinical Trial
REC	Research Ethics Committee
RN	Research Nurse
SAE	Serious Adverse Event
SCTU	Southampton Clinical Trials Unit
SMG	Study Management Group
SSAG	Study Specific Advisory Group
TMF	Trial Master File
TSC	Trial Steering Committee
WBC	White Blood Count
YPAG	Young Persons Advisory Group

KEYWORDS

appendicitis; appendicectomy; abdominal pain; core outcome set; patient and public involvement; randomised controlled trial; evidence based medicine; qualitative research

STUDY SYNOPSIS

Short title/Acronym:	CONTRACT
Full title:	CONservative Treatment of Appendicitis in Children – a randomised controlled Trial (Feasibility)

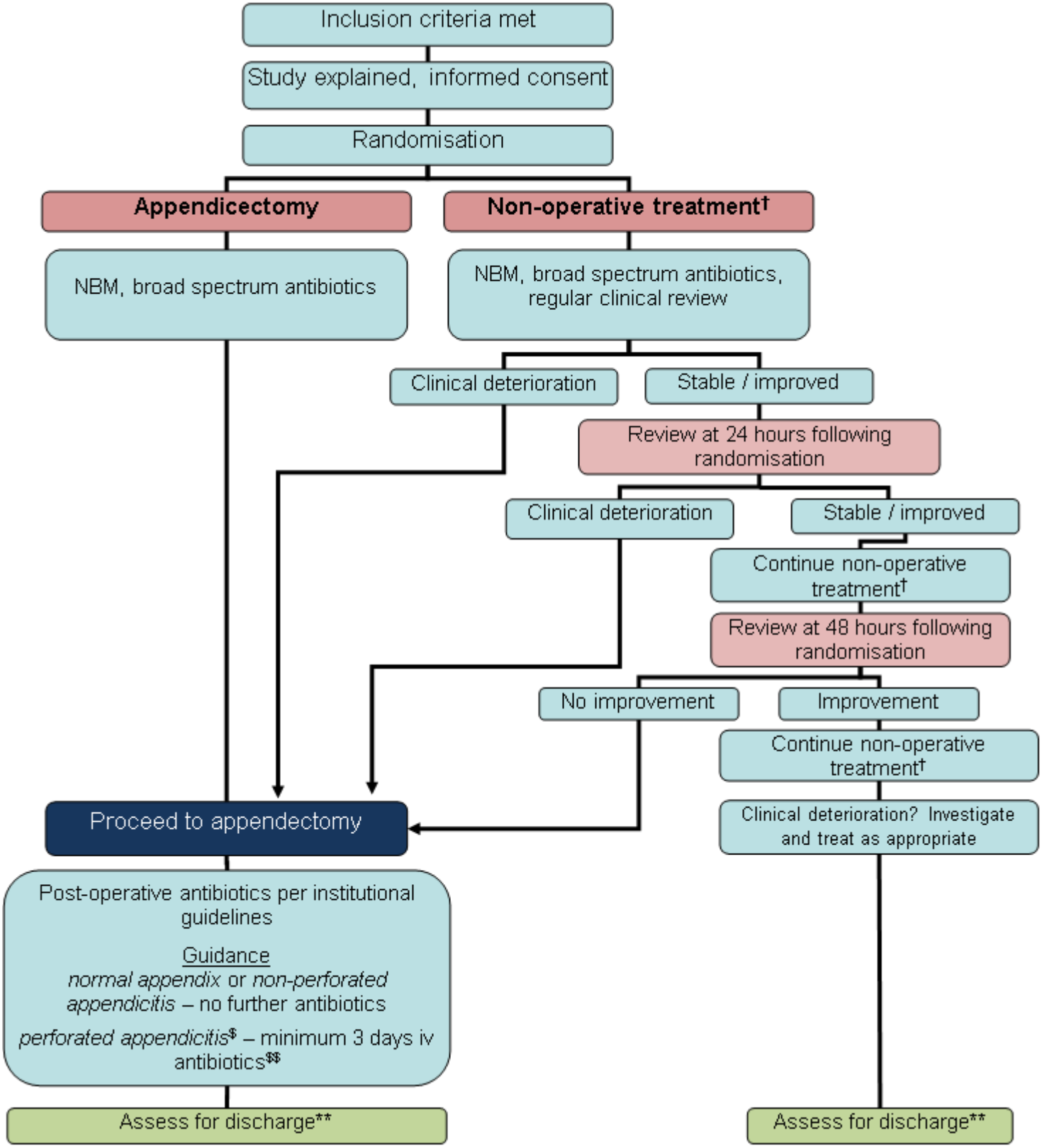
Study Phase:	Feasibility
Population:	Children (aged 4-15 years) with a clinical diagnosis of acute uncomplicated appendicitis
Primary Objective:	Assess whether it is feasible to conduct a multi-centre randomised controlled trial testing the effectiveness and cost-effectiveness of a non-operative treatment pathway for the treatment of acute uncomplicated appendicitis in children
Secondary Objective:	• Assess the willingness of parents and children to be enrolled in, and surgeons to recruit to a randomised study comparing operative versus non-operative treatment and identify anticipated recruitment rate • Identify strategies to optimise surgeon-family communication to inform the future RCT • Enhance the design of a future RCT from the perspectives of stakeholders at participating sites (children, parents, surgeons and nurses) • Identify what core outcomes family members and surgeons regard as important to measure in a future RCT and to develop a core outcome set • Assess the equipoise and willingness of UK paediatric surgeons to participate in a future RCT • Generate data to allow for the design of a definitive RCT, including sample size calculation and identification of key cost drivers and other parameters necessary to perform a full economic analysis • Examine clinical outcomes of children with acute appendicitis treated without an operation including an initial assessment of efficacy and safety of this treatment pathway in our centres • Ensure the whole of the research programme is well informed by a group of children and parents, our SSAG
Rationale:	Currently, there is no good evidence to inform surgeons, patients and parents whether non-operative treatment of acute uncomplicated appendicitis in children is effective and cost effective.
Study Design:	Mixed methods feasibility study comprising: • Randomised controlled trial • Embedded and parallel qualitative and survey study • Development of core outcome set
Sample size :	No target as feasibility of recruitment being tested – patients will be recruited over 12 months (approx. 65 pts)
Treatment/Intervention:	A. Non-operative treatment pathway (broad-spectrum antibiotics and active observation) B. Appendicectomy

URL for Database:	https://login.imedidata.com/login

URL for randomisation:	www.formsvision.com

Primary Study Endpoints:	Proportion of eligible patients recruited to the study over 12 months
Secondary Study Endpoints:	Audio-recordings of recruitment consultations and qualitative interviews Core Outcome Set Survey work Clinical outcomes of clinical trial Review of SSAG activity
Total Number of Sites:	3 paediatric surgical teaching hospitals

STUDY SCHEMA



NBM = nil by mouth

† non-operative treatment = NBM/sips for initial 12h minimum then advance diet as tolerates; iv antibiotics 24h minimum, change to oral once afebrile for 24h, total course 10 days; analgesia

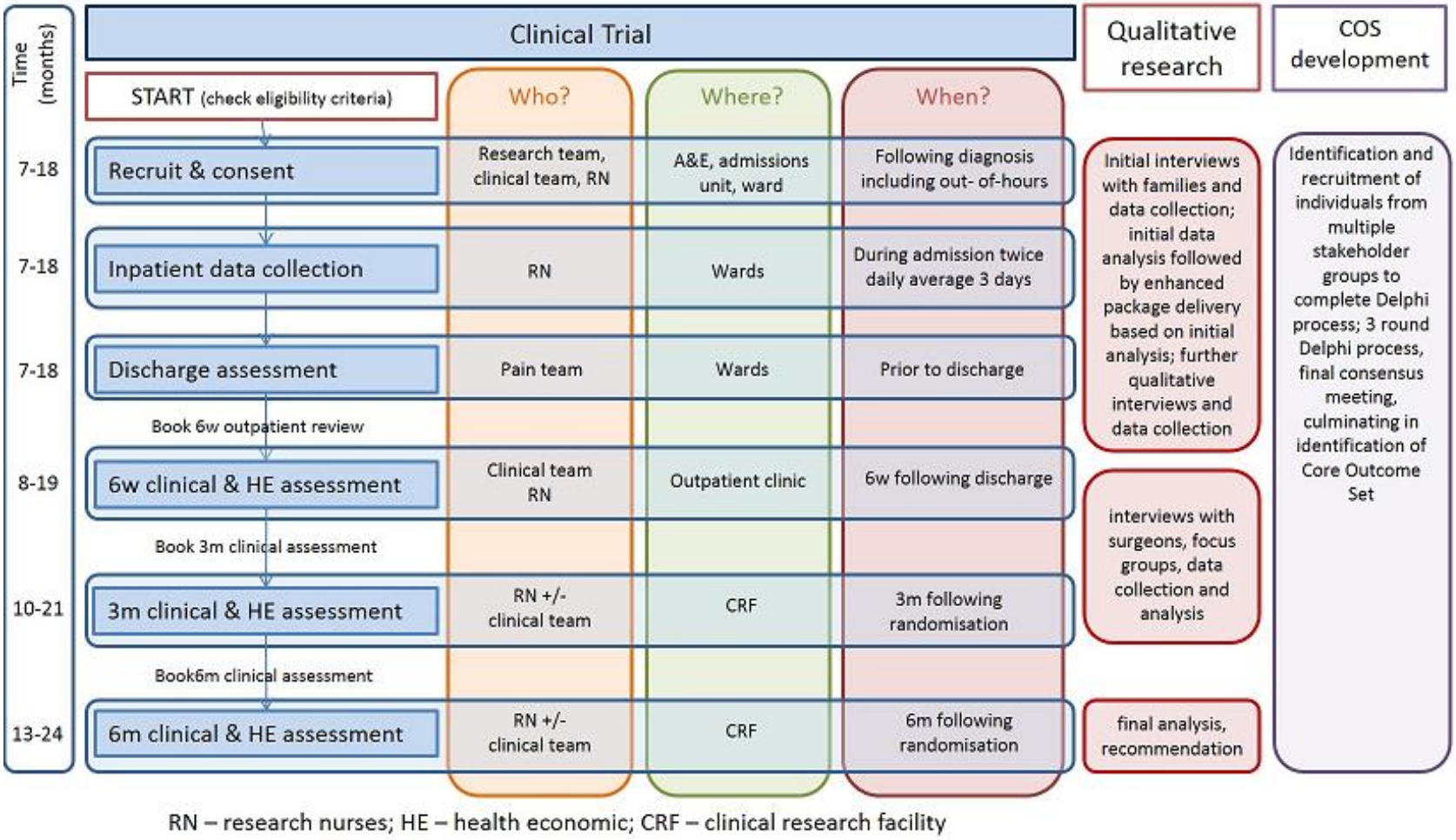
* appendicectomy group – no routine use of nasogastric tube or urinary catheter, advance diet as tolerates

$ defined as either seeing a hole in the appendix or faecal matter/faecolith in the peritoneal cavity

$$ continue iv antibiotics until afebrile for 24h, then change to oral; minimum 5 days total antibiotics

** criteria for discharge include: vital signs within normal limits, tolerating light diet, adequate oral analgesia, mobile

OVERALL STUDY SCHEDULE



RN – research nurses; HE – health economic; CRF – clinical research facility

SCHEDULE OF OBSERVATIONS AND PROCEDURES FOR CLINICAL TRIAL

Visit / Time point:	**Baseline**	**Randomisation to 24 hours**	**24 hrs to 48 hrs**	**48 hrs to Discharge**	**Discharge to 2 weeks**	**Visit 1 6 weeks**	**Visit 2 3 months**	**Visit 3 6 months**
Screening log	**X**							
Informed Consent	**X**							
Eligibility evaluation	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Medical History	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Diagnostic Tests (blood test – Total WBC /CRP /Neutrophil, CT scan, Ultrasound)	**X**							
Pregnancy Test	**X**							
Physical Exam (Abdomen exam)	**X**					**X**		
Vital Signs (Temperature)	**X**							
Appendicectomy (where appropriate)		**X**						
Clinician Assessment		**X**	**X**					
Antibiotic log		**X**	**X**	**X**	**X**	**X**	**X**	**X**
Discharge Assessment				**X**				
Concurrent Medication (Pain relief only)		**X**	**X**	**X**	**X**	**X**	**X**	**X**
Adverse Events		**X**	**X**	**X**	**X**	**X**	**X**	**X**
Health Economics – resource use	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
EQ5D / CHU-9D	**X**			**X**	**X**	**X**	**X**	**X**
Patient Diary Card					**X**			
Client Service Receipt Inventory (CSRI)						**X**		**X**
Qualitative Interviews						**X**		

NB: The Participant/legal representative is free to withdraw consent at any time without providing a reason. When withdrawn, the participant will continue to receive standard clinical care. Follow up data will continue to be collected (unless the participant/legal representative has specifically stated that they do not want this to happen).

1 INTRODUCTION

1.1 BACKGROUND

Acute appendicitis is the commonest surgical emergency in children [12]. The lifetime risk of developing appendicitis is 7-8% and the commonest age for developing appendicitis is in the early teens. Appendicectomy is considered the gold standard treatment for acute appendicitis by most surgeons. As a result in the year 2012-13 (most recent period with available data) there were 9,035 emergency appendicectomies in England in children.

Many parents find the proposal that their child needs emergency surgery frightening and one they are keen to avoid if an alternative is available. Our PPI work confirms this. Families frequently ask "*Does my child really need an operation?*"

Although appendicectomy is usually a simple procedure, it requires a general anaesthetic and an abdominal operation with inherent risks. Complication rate of appendicectomy (including wound infection, intra-abdominal abscess, and adhesional small bowel obstruction) is up to 25% [13] with a need for hospital readmission in 4-5% [14, 15]. A contemporary estimation of these risks is available from the National Appendicectomy Audit, a nationwide audit of outcomes of appendicectomy for acute appendicitis in 19 Specialist Paediatric Surgery Centres in the UK co-ordinated by the Chief Investigator [9]. Over a 2 month period, 242 appendicectomies for acute appendicitis were performed. The negative (histologically normal) appendicectomy rate was 10.3% and the 30-day adverse event rate (a composite of readmission, re-intervention, pelvic collection and wound infection) was 15.3%.

The financial burden of paediatric appendicitis in England is in excess of £21 million per year. Appendicectomy requires significant resource use including need for out-of-hours surgery (45% of all paediatric appendicectomies were performed between 1800 and 0800 in the recent audit).

An alternative approach to the treatment of children with acute appendicitis would be treatment with antibiotics and without an appendicectomy. Whilst there is growing scientific interest in the use of non-operative treatment with antibiotics, we do not yet know whether this approach is safe and effective. However, there are several potential benefits to a non-operative approach over surgery including:

- avoiding the trauma, physiological stress, psychological distress and physical scarring of an operation
- avoiding complications as a result of surgery or general anaesthesia
- reduced NHS resource use with potential for significant savings if non-operative treatment is effective (over £500 per case based on HRG tariff).

However, such an approach would only be acceptable if antibiotic treatment is safe, successful in the majority of cases and the risk of recurrent appendicitis is low.

It has been known for some time that acute appendicitis can been treated successfully by antibiotics alone, in the context of remote environments without surgical service capability [16]. However, the role of non-operative treatment as primary therapy has only recently come under consideration in developed healthcare systems initially in adults [13, 17-23] and more recently in children [1, 4, 5].

Although studies in adults may be extrapolated to children, to do so is problematic since there are key differences in appendicitis occurring in adults compared to children. A paediatric RCT is necessary since appendicitis presents differently in children and adults, the intra-abdominal inflammatory response is different in adults and children [33, 34] and may be more amenable to antibiotic treatment alone, and the psychosocial and economic impact of appendicitis in children affects the whole family, rather than just the individual.

There is just one RCT, recently performed in Sweden, in which the Chief Investigator and one co-investigator (SE) were involved in the design, running and analysis, comparing non-operative

treatment with antibiotics with appendicectomy in children with acute appendicitis [5]. Fifty children (aged 5-15 years) with acute non-perforated appendicitis were randomised to antibiotics (n=24) or appendicectomy (n=26). All children in the surgery group had histopathologically-confirmed acute appendicitis and none experienced a significant surgical complication. In the antibiotic group, 2 of 24 underwent appendicectomy within the time of primary antibiotic treatment, and 1 further child required appendicectomy for histologically-proven, recurrent acute appendicitis 9 months later. Of eligible participants, the recruitment rate was 40%, the drop-out rate following treatment allocation was 2% (1 patient) and no patient was lost to follow-up by 1 year. This pilot study was not powered to compare the efficacy of antibiotics vs surgery, but was conducted to inform the design of a large multicentre RCT including North America which is still in planning stage.

Safety of non-operative treatment: importantly none of the existing studies of non-operative treatment of acute uncomplicated appendicitis in children have identified any safety concerns regarding the intervention [1-6].

Recurrent appendicitis is a consideration in children who receive non-operative treatment that is not applicable to children treated with appendicectomy. In adults [17-20, 25] the incidence of recurrence (within 1 year) is around 15%. The incidence of recurrence in children is largely unknown although the recent pilot study of non-operative treatment of appendicitis in children with 1 year follow-up reported a recurrence rate of 5% [5]. A systematic review of recurrent appendicitis following successful non-operative treatment of an appendix mass (a distinct clinical entity from acute appendicitis) in children estimated an incidence of 20% [35]. These data are the closest we have to an estimate in children.

1.2 RATIONALE AND RISK BENEFITS FOR CURRENT STUDY

Currently, there is no good evidence to inform surgeons, patients and parents whether non-operative treatment of acute uncomplicated appendicitis in children is effective and cost effective. To determine this we intend to perform a multicentre prospective randomised controlled trial. Prior to such a trial, a feasibility study is necessary to determine whether recruitment to a large RCT is feasible, to refine methodology and outcomes, and engage with stakeholders.

We have also embedded qualitative methods within this trial to optimise recruitment and enhance trial design and our treatment approach [38, 39]. We refer to this qualitative study as the 'Communication Sub-study' in the Information Sheets and Consent Forms to assist patient and family understanding.

As no COS of relevance to trials involving non-operative treatment of children with acute appendicitis currently exists [53], we will define a COS, involving multiple stakeholders (surgeons, children and parents) in the process. This will ensure that the outcomes we measure in our planned RCT will have the most significant impact and are relevant not only to surgeons but also to children and their families.

2 STUDY OBJECTIVES

In the long term, we aim to determine if it is effective and cost-effective to treat children with acute uncomplicated appendicitis with a non-operative treatment pathway instead of appendicectomy. This will require a large, multicentre non-inferiority RCT.

First we will perform this feasibility study, the aim of which is to answer the research question:

Is it feasible and acceptable to conduct a multi-centre randomised controlled trial testing the effectiveness and cost-effectiveness of a non-operative treatment pathway for the treatment of acute uncomplicated appendicitis in children?

	Objective	Endpoint used to evaluate
Primary:	Assess whether it is feasible to conduct a multi-centre randomised controlled trial testing the effectiveness and cost-effectiveness of a non-operative treatment pathway for the treatment of acute uncomplicated appendicitis in children	Proportion of eligible patients recruited to the study over 12 months
Secondary:	Assess the willingness of parents and children to be enrolled in, and surgeons to recruit to, a randomised study comparing operative versus non-operative treatment and identify anticipated recruitment rate	Embedded qualitative study
	Identify strategies to optimise surgeon-family communication to inform the future RCT	Embedded qualitative study
	Enhance the design of a future RCT from the perspectives of stakeholders at participating sites (children, parents, surgeons and nurses)	Embedded qualitative study
	Identify what core outcomes family members and surgeons regard as important to measure in a future RCT and to develop a core outcome set	Core Outcome Set
	Assess the equipoise and willingness of UK paediatric surgeons to participate in a future RCT	Survey work
	Generate data to allow for the design of a definitive RCT, including sample size calculation and identification of key cost drivers and other parameters necessary to perform a full economic analysis	Clinical outcomes of clinical trial including response rate to initial treatment pathway, complications and rate of recurrent appendicitis
	Examine clinical outcomes of children with acute appendicitis treated without an operation including an initial assessment of efficacy and safety of this treatment pathway in our centres	Clinical outcomes of clinical trial (as above)
	Ensure the whole of the research programme is well informed by a group of children and parents, our SSAG	Review of Study Specific Advisory Group (SSAG) activity

3 STUDY DESIGN

The proposed work comprises a number of inter-related elements:

A. A randomised controlled feasibility trial of children comparing a non-operative treatment pathway with appendicectomy. Both groups of children will receive broad spectrum antibiotics from the point of enrolment; one group of children will undergo urgent appendicectomy, the other will be treated non-operatively with continuation of broad spectrum intravenous antibiotics. A standardised treatment pathway (See Trial Schema) will be used for patients in both arms of the study. All patients will be followed-up with visits at 6 weeks, 3 months and 6 months.

B. A detailed program of qualitative and quantitative research embedded within the above feasibility trial which will be used to optimise the design and conduct of a future RCT of non-operative treatment versus appendicectomy in the treatment of acute uncomplicated appendicitis in children.

C. The development of a COS for the non-operative treatment of children with uncomplicated acute appendicitis for use in our future trial and by the wider research community (see appendix A).

3.1 DEFINITION OF END OF STUDY

The study will end once the final participant recruited has completed the 6 month follow up period.

4 SELECTION AND ENROLMENT OF PARTICIPANTS

4.1 CONSENT

Eligible participants will be identified by the clinical team at time of diagnosis of acute appendicitis.

Recruitment will be performed by surgeons and supported by research nurses since our preparatory work, with the NIHR CRN (Children) young person's advisory groups (YPAGs), has indicated that parents do not feel it appropriate to be recruited into this trial by anyone other than a surgeon. The CRN has also indicated that they do not think it is appropriate for nurses to recruit to this study alone due to the nature of the intervention which will challenge commonly-held beliefs about appendicectomy as best treatment for appendicitis, and the relatively short timeframe necessary for a decision to be made. We will utilise members of the clinical team (Specialist Surgical Trainees and Consultants) to recruit patients to the study in conjunction with research nurses. Recruitment capacity will therefore be available 16 hrs per day. This provides a realistic approach for a future multicentre trial.

Parents will be approached by a member of the surgical team and a research nurse who will explain the study to them and invite them to participate. Prior to this discussion verbal permission will be taken for the recruitment discussion to be voice recorded. The CONTRACT study will be explained to parents and children with the aid of age specific information sheets and a short video presentation. Written consent for inclusion in the clinical trial will be obtained from all families including assent (as opposed to consent) from children age 12 years or older who wish to give it (as suggested by our pre-study PPI work with young people). Consent for CONTRACT will be sought only after a full explanation of the study has been given and an information leaflet offered. At this time, written consent will also be sought for keeping and including the voice recording of the recruitment conversation in the qualitative analysis for the Communication Sub-study. If consent to keep the recording is not provided then the recording will be deleted.

We are sensitive to the need for participants and families to be given adequate time to consider the study yet there is also a need for a decision to be made within a short period of time. Whilst appendicectomy is not typically a true surgical emergency it is considered an urgent procedure. The consent process is therefore 'time-constrained' rather than truly urgent. Participants will be made aware of this and consent will be obtained within a maximum of 4 hours of first discussion of the study. The research process will never impede on provision of safe and effective patient care.

We will provide an educational package to clinical staff at each centre. This will include educational evenings at or near each centre to which all members of the clinical team (core and specialist surgical trainees, research nurses and consultant surgeons); a short video to be shown to potential participants during the recruitment process; age appropriate PIS and consent form.

The right of the participant to refuse to participate without giving reasons will be respected. After the participant has entered the study the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the

participant's best interest, but the reasons for doing so should be recorded. In these cases the participant remains within the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

4.2 INCLUSION CRITERIA

- Child age 4 – 15 years (<16 years and >3 years)
- Clinical diagnosis, either with or without radiological assessment, of acute appendicitis which prior to study commencement would be treated with appendicectomy
- Written informed parental consent, with child assent if appropriate

4.3 EXCLUSION CRITERIA

- Clinical signs or radiological findings to suggest perforated appendicitis
- Presentation with appendix mass
- Previous episode of appendicitis or appendix mass treated non-operatively
- Major anaesthetic risk precluding allocation to the appendicectomy arm
- Known antibiotic allergy preventing allocation to non-operative treatment arm
- Antibiotic treatment started at referring institution (defined as 2 or more doses administered)
- Cystic fibrosis (there is a higher background incidence of appendicitis in this population and they are at an increased risk of recurrence. Therefore, there is a lack of equipoise between treatment arms for this group of children)
- Positive pregnancy test
- Current treatment for malignancy

4.4 SCREENING FAILURES

The Research Nurse in each Centre will complete a screening log detailing each time a potential participant is approached and document their decision to participate in the CONTRACT Study. Patients who are screen failures will have their initials, month and year of birth, and reason for failure recorded on the screening log. The screening log will be discussed with the surgical team on a daily basis. Screening logs will be sent to the TM on a weekly basis.

4.5 REGISTRATION/RANDOMISATION PROCEDURES

Once eligibility for the trial is confirmed and informed consent received, patients will be enrolled in the study and randomised to a treatment group (1:1 ratio) via an independent, web-based system (TENALEA). This online system allows for instant assignment to either the Appendicectomy or Non-Operative treatment group, 24 hours per day.

This service will be provided by the Southampton Clinical Trials Unit, with telephone back-up during office hours.

5 STUDY OBSERVATIONS AND PROCEDURES

5.1 SCREENING PROCEDURES

Children with a diagnosis of acute uncomplicated appendicitis will be identified by the clinical team at the time of diagnosis. Their eligibility for the study will be confirmed by the research nurse at each centre as soon as possible after being informed of the patient.

Clinicians can use a combination of diagnostic tools as part of standard practice to confirm the child's diagnosis, including but not limited to a physical exam, medical history, temperature check, ultrasound, CT scan, blood and pregnancy tests. If any of these are used to diagnose the child, it will be recorded retrospectively on the CRF database once consent and randomisation has been completed. The results of the pregnancy and blood tests will be recorded on the database, specifically total white blood count, C-Reactive Protein and Neutrophils. The Alvarado Score will also be recorded as a clinical descriptor i.e. it will not be used for diagnostic purposes.

5.2 STUDY PROCEDURES

5.2.1 Randomisation to Discharge

Informed consent and randomisation should happen within 4 hours of the initial trial discussion. Upon randomisation, the appropriate treatment pathway should be administered immediately, as detailed below.

Non-operative treatment group

This treatment pathway will comprise fluid resuscitation, a minimum of 24 hours broad spectrum intravenous antibiotics (as per local policies), a minimum period of 12 hours 'nil by mouth' and regular clinical review to detect symptoms and signs of significant clinical deterioration including, but not limited to, increasing fever, increasing tachycardia, and increasing tenderness.

Children receiving non-operative treatment, who, in the opinion of the consultant surgeon in charge of their care have clinically deteriorated such that urgent appendicectomy is mandated, will undergo appendicectomy at any stage. A review will be performed at approximately 24 hours following randomisation and any child deemed to have significantly deteriorated will undergo urgent appendicectomy. Those who are stable or clinically improving will continue with non-operative treatment. Those who are not showing clinical signs of improvement at approximately 48 hours following randomisation will undergo urgent appendicectomy. These decision points will be made based on the clinical judgement of the treating consultant as is current practice rather than on any predefined set of criteria for which evidence does not currently exist.

Children who receive an appendicectomy for failure of non-operative treatment will be treated post-operatively according to a standardised treatment regime already in use at our institutions and identical to that to be used in children in the appendicectomy treatment group (see below). Reason for failure will be recorded on the CRF database.

After the initial 12-hour period of 'nil by mouth', oral intake will be advanced as tolerated. Children, in whom non-operative treatment is successful, will receive a minimum of 24 hours intravenous antibiotics and then be converted to oral antibiotics (as per local policies) once they are afebrile for 24 hours and tolerating oral intake.

Criteria for discharge home will be: vital signs within normal limits for age, afebrile for ≥24 hours, tolerating light diet orally, have adequate oral pain relief and be mobile. They will receive a total course of 10 days antibiotics following randomisation, unless decided otherwise by treating clinician. If more than 10 days oral antibiotics are administered, this will be recorded (including reason). Children who receive non-operative treatment will not be routinely offered interval appendicectomy but will be counselled about the risk of recurrence using best available data.

The following data will be recorded for children randomised to the non-operative treatment arm. This can be collected retrospectively from patient's notes:

- Decision to continue with non-operative treatment – as per clinician review at approximately 24 hours and 48 hours
- Use of antibiotics - both IV and oral
- Use of pain relief - Paracetamol, NSAIDs, Morphine
- Adverse events / effects relating to antibiotic use

For children who received an appendicectomy for failure of non-operative treatment:

- Details of decision to change treatment
- Details regarding the appendicectomy – type of procedure, operative findings, complications (both intra- and post-operative) date, time etc.

Appendicectomy group

Children allocated to appendicectomy will undergo either open or laparoscopic appendicectomy at the surgeon's discretion. The procedure may be performed by a suitably experienced trainee (as is routine current practice) or a consultant. As per current routine practice, a peritoneal microbiology swab will be taken at the time the peritoneum is first opened or from the appendix and any peritoneal fluid sent for microbiological culture. The results of this swab will be recorded.

Participants will receive intravenous antibiotics from the time of randomisation and be treated post-operatively with intravenous antibiotics according to existing institutional protocols. The following recommended regime is intended to guide practice: children with uncomplicated acute appendicitis or a macroscopically normal appendix will receive no further antibiotics; children with a perforated appendix (defined as a faecolith or faecal matter within the peritoneal cavity or visualisation of a hole in the appendix [59]) will continue to receive intravenous antibiotics for a minimum of 3 days, and will receive a minimum total course of antibiotics of 5 days (intravenous and oral). It is not possible to completely 'protocolise' the duration of antibiotics therapy due to anticipated variation in intra-operative findings and in response to treatment. The type of antibiotics used will be identical to those used in the non-operative treatment arm within each centre (see above). Any child failing to respond to these first line antibiotics will be treated as is clinically appropriate with a longer course of antibiotics or a change in antibiotic therapy with choice of antibiotic determined by intra-operative swab or fluid culture.

Post-operatively, children with uncomplicated acute appendicitis or a normal appendix will not routinely have a nasogastric tube, nor a urinary catheter; they will receive oral intake as tolerated after surgery. Criteria for discharge home will be identical to those in the non-operative treatment group.

The following data will be collected for children randomised to the Appendicectomy arm. This can be collected retrospectively from patient's notes:

- Details regarding the appendicectomy – type of procedure, operative findings, complications (both intra- and post-operative) date, time etc.
- Use of antibiotics - both IV and oral
- Use of pain relief - Paracetamol, NSAIDs, Morphine
- Adverse events / effects relating to antibiotic use

5.2.2 Discharge Assessment

Once a decision to discharge the child has been made, a member of the clinical team who has not been directly involved in the child's treatment will be asked to complete a discharge assessment. This assessor will not have prior knowledge of the treatment pathway assigned to the child and will not know which treatment they received. Upon completion of the discharge assessment, they will "guess" which treatment the child received. If the assessor should become unblinded during the assessment, this will be recorded on the CRF database.

All participants, across both treatment groups, will be provided with a discharge pack. This pack will contain a leaflet highlighting concerning symptoms and action to be taken should any of them occur, a patient diary card, a questionnaire booklet and details on how and when to complete. The discharge leaflet will also include advice to contact a member of the medical team at each participating hospital (with relevant contact details) or the participants GP in an emergency and the telephone number of the research nursing team at each site for less urgent concerns. Finally, we will write to the participant's GP to inform them of their patient's inclusion in the study.

Patients in both treatment arms will be followed-up for 6 months following randomisation but we will seek consent for further follow-up including the recording of patient / parent contact information for this purpose. See section 5.3 for more information regarding follow up.

The following data will be collected at discharge:

- Resolution of symptoms – date / time of decision to discharge
- Date and time of first eating
- Total number of cannulae used – antibiotics and fluids
- Outcome of blinded assessment (where possible)
- Adverse events

5.2.3 EMBEDDED QUALITATIVE STUDY OF RECRUITMENT AND TRIAL DESIGN

Qualitative research methods embedded into this feasibility trial as part of the Communication Sub-study to investigate the acceptability to families of the recruitment consultation, trial interventions and wider trial processes, with the aim of optimising informed consent and recruitment. To identify potential barriers to recruitment, and improve informed consent we will examine the process and experience of CONTRACT at participating sites informed by transcribed audio-recordings of:

1. Recruitment consultations that take place between families, surgeons and research nurses (recruiters) during which information on the trial is provided and discussed before seeking consent for trial entry
2. Follow-up qualitative interviews with families (children and parents) purposively sampled for maximum diversity to include those who accept, decline or withdraw from the trial

3. Follow-up qualitative interviews with recruiters
4. Qualitative interviews with other members of the clinical teams caring for children including nurses and non-participating surgeons

Using data from 1, 2 and 3 above we will compare what was said during recruitment consultations with families' and recruiters' interpretations of these consultations. We will use these comparisons to identify the circumstances, topics or phrases that are associated with difficulties in communicating the study. Qualitative interviews with other members of the clinical teams (4), will examine wider opinions and beliefs about the trial, and the interventions offered in the trial.

Informed by analyses of these data, we will work with recruiters on a dynamic basis to identify strategies to enhance communication about CONTRACT. Findings will be fed back to the TSC and local investigators and suggestions made to change aspects of design, conduct and organisation or training that could be used to improve our planned future trial. Using this iterative process we will enhance and refine recruitment to CONTRACT whilst the trial is in progress [60, 61].

The deliverable will be the cumulative lessons learnt from this work to enhance the information provided to parents and patients (written and video) for a future RCT and inform development of a recruitment 'hints and tips' educational package.

Recording of recruitment conversations

Recruiters will seek verbal permission to audio-record trial recruitment consultations from families whom they approach for CONTRACT. The purpose of the audio-recording these consultations will be briefly outlined and recording device activated if permission is given. At the end of the recruitment consultation recruiters will discuss the qualitative study with the family in more detail and seek signed consent for the audio-recording to be included in the analysis. Recordings from families who decline the inclusion of the audio-recording will be erased at the end of the consultation. Permission to pass the families' contact details to the qualitative researcher will be sought. An experienced qualitative researcher will contact families within a few weeks of discharge from hospital to explain the study further and invite them to be interviewed.

Interviews with children and parents

Semi-structured topic guided interviews with families (parents/carers of children aged 4-15 years and children/young people aged 7-15 years) will usually be carried out within 1-4 weeks after hospital discharge. An information sheet on the interviews will be provided in advance and consent/assent will be sought. Children will be interviewed using participatory techniques where appropriate to ensure interviews are engaging and developmentally suitable for children with different levels of maturity. All children will be given the opportunity of being interviewed alone or with their parent present if they prefer.

Interviews with parents and children will investigate:

1. Prior experience of the study interventions; beliefs, expectations and preferences about the interventions before allocation
2. Views on the process of randomisation, and acceptability of the interventions and suggestions for improving the trial design and recruitment process.
3. Outcomes families think are important to measure, and any concerns they have about their child's future well-being.

We are particularly interested in understanding barriers to participation and will interview (subject to informed consent) those who choose not to participate in the trial, or who do not accept treatment allocation at randomisation. Topic guides will be adapted so that they are appropriate for parents and children.

The qualitative interviewers will ensure that interviews are conversational and their pace, sequencing and duration is shaped by participants. To minimise the risk of obtaining generalised or idealised accounts we will routinely review consultation transcripts before the interviews to develop specific prompts as necessary to explore family perceptions of individual recruitment consultations. Topic guides will be periodically revised in the light of the developing analysis to ensure exploration of important but unanticipated issues.

Face-to-face interviews with families will take place at a location of their choosing, usually in their homes, although they will have the option of being interviewed via Skype or telephone if they prefer. Interview topic guides that are used to steer the interviews will mainly comprise open ended questions for participants to describe the recruitment process in their own words and their subsequent experiences of the trial. Interview topic guides will be appropriate to whether they entered and remained in the trial, entered and withdrew or declined.

Interviews with recruiters and wider clinical staff

Interviews with recruiting surgeons and nurses will usually take place after they have conducted at least one CONTRACT recruitment consultation. These interviews, which will usually take place in a private room in participants' workplaces or by telephone, will follow a similar course to the family interviews, but will be steered by a separate topic guide. For recruiters for whom audio-recorded consultations are available, interviews will be informed by a review of a recording from a recent consultation to explore their goals for the consultation in the light of their approach to communication.

All recruiters and clinical staff will be prompted to describe their views and experiences of CONTRACT. For those with formal roles in recruiting, interviews will explore accounts of deciding which families to approach about the trial. For all staff, interviews will examine experiences of discussing the trial with families at recruitment and subsequently; and what information children and parents require to inform their decision-making. Recruiters' and clinical staff members' views about which outcomes are important to measure will also be explored during the interviews.

5.2.4 ASSESSING THE EQUIPOISE OF UK PAEDIATRIC SURGEONS: MIXED METHODS STUDY

We will assess the equipoise and views about a future main trial among paediatric surgeons at non-participating sites using a mixed survey and qualitative design. An online survey will be designed, and will examine surgeons' equipoise over our research question and their potential willingness to invite their patients to be randomised to a trial comparing surgery versus non-operative treatment for acute uncomplicated appendicitis in children. The sample frame will comprise membership lists of the British Association of Paediatric Surgeons (BAPS) and other UK consultant Paediatric surgeons from the 29 UK Specialist Paediatric Surgical centres. Data will be analysed quantitatively. Qualitative interviews with a maximum diversity sub-set (geographical, hospital setting, training level/ research experience, ethnicity) of survey respondents will contextualise the survey responses and explore what knowledge has informed their potential willingness or reluctance to invite patients to be randomised, their position in relation to equipoise and what other considerations might influence their involvement in a future trial. We will further explore

suggestions regarding the design of the future trial, obstacles to be overcome and important outcomes in 2 focus groups. Focus group participants will be selected based on survey responses to create groups with diverse views to allow us to explore a wide range of opinion.

5.2.5 EMBEDDED HEALTH ECONOMICS STUDY

We will collect cost data during the in-patient phase of treatment and also identify costs associated with healthcare resource use and societal costs (e.g. days off school, parental days off work) during the 6 month follow-up period using a modified version of the Client Service Receipt Inventory (CSRI) questionnaire and the patient diary card. The patient diary card will cover the 2 week period immediately following discharge while the CSRI will be collected at the 6 week and 6 month follow up appointments.

To enable detection of any effect of our intervention on QoL we will collect data using preference-based quality of life measures. We will assess the appropriateness of using the QALY framework in the future RCT, as well as testing and identifying the most suitable QoL instrument. The proposed measures are the child friendly version of the EQ-5D 5L and the CHU-9D, a new quality of life measure specifically designed for use in studies with children [68, 69]. The EQ-5D-5L comprises the same 5 dimensions as the EQ-5D-3L but 5 levels of severity, which is considered to significantly increase reliability and sensitivity (discriminatory power) [87, 88]. Both measures will be obtained from parental/carer proxy responses. Children aged 7 and over can also complete these if they wish. We will collect both QoL measures at baseline; discharge; 2 weeks (provided to patient at discharge), to determine any short term difference in QoL that may be missed at 6 week follow-up); 6 weeks; 3 months; and 6 months, to define the most appropriate timing of assessment in relation to other health outcomes.

5.3 FOLLOW UP

Follow-up appointments will take place at 6 weeks, 3 months and 6 months following discharge in the outpatient clinic or Clinical Research Facility at each participating centre. There is also the potential for the 3 month and 6 month appointments to be completed over the phone if a face-to-face appointment is not possible. Data will be collected prospectively to ensure high accuracy. These visits will ensure completeness of the dataset collected, in particular time to return to daily activities, recurrent appendix-related problems (including unexplained abdominal pain and recurrence) and resource use data.

The following data will be collected at all follow up appointments:

- QoL questionnaires (EQ-5D and CHU-9D)
- CSRI (6 week and 6 month appointments only)
- Readmission relating to appendicitis / Recurrent appendicitis
- Health service resource use relating to appendicitis
- Complications since discharge

Data specifically collected at 6 week follow up appointment:

- Histology findings for children who received an appendicectomy
- Outcome of physical exam (if completed as part of standard care)

We will also seek consent from parents to contact them at yearly intervals by telephone / e-mail to find out if their child has had recurrent appendicitis during a longer duration of

follow-up, up to a maximum of 5 years. We will request consent to store personal data (telephone number and e-mail address) securely for the purposes of this study only. This activity is outside of the current funding remit.

5.4 DEVIATIONS AND SERIOUS BREACHES

Any study protocol deviations/violations and breaches of Good Clinical Practice occurring at sites should be reported to the SCTU and the local R&D Office immediately. SCTU will then advise of and/or undertake any corrective and preventative actions as required.

5.5 STUDY DISCONTINUATION

In consenting to the study, participants have consented to the study intervention, follow-up and data collection. Participants may be discontinued from the study procedures at any time.

Reasons for study discontinuation

Participants may be discontinued from the study in the event of:

- Clinical decision, as judged by the Principal Investigator or Chief Investigator
- Withdrawal of informed consent (participant's decision to withdraw for any reason)
- Serious adverse event which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the participant
- Any clinical adverse event, laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the participant
- Participant non-compliance

Full details of the reason for study discontinuation should be recorded in the eCRF and medical record.

5.6 WITHDRAWAL

The participant / legal representative is free to withdraw consent from the study at any time without providing a reason.

If a participant withdraws from the trial prior to receiving the allocated intervention they will be treated as determined by the consultant in charge of the child's care.

Investigators should explain to patients the value of remaining in study follow-up and allowing this data to be used for trial purposes. Where possible, patients who have withdrawn from study treatment should remain in follow-up as per the trial schedule. If patients additionally withdraw consent for this, they should revert to standard clinical care as deemed by the responsible clinician. It would remain useful for the study team to continue to collect standard follow-up data and unless the patient explicitly states otherwise, follow-up data will continue to be collected.

Details of study discontinuation (date, reason if known) should be recorded in the eCRF and medical record.

5.7 PROHIBITED AND RESTRICTED THERAPIES DURING THE STUDY

None

5.8 BLINDING AND PROCEDURES FOR EMERGENCY UNBLINDING

Due to the nature of the interventions in this study there will be no blinding of participants or investigators.

6 SAFETY

6.1 DEFINITIONS

Adverse Event (AE): any untoward medical occurrence in a participant or clinical study participant which does not necessarily have a causal relationship with study treatment or participation.
An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the study treatment or participation (regardless of causality assessments).

Serious Adverse Event (SAE) or **Serious Adverse Reaction** is any untoward medical occurrence or effect that :

- **Results in death**
- **Is life-threatening** – *refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe*
- **Requires hospitalisation, or prolongation of existing hospitalisation**
- **Results in persistent or significant disability or incapacity**
- **Is a congenital anomaly or birth defect**
- Other important medical events***.

*'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
**Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute an SAE.
***Other important medical events May also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.
Note: It is the responsibility of the PI or delegate to grade an event as 'not serious' (AE) or 'serious' (SAE).

6.2 SERIOUSNESS

All adverse events that fulfil the criteria definition of 'serious' in protocol section 6.1, must be reported to SCTU using the Serious Adverse Event Report Form – Non-CTIMP. All SAEs must be reported immediately by the PI at the participating centre to the SCTU unless the SAE is specified as not requiring reporting (see section 6.2.1 below).

6.2.1 Exceptions:

For the purposes of this study, the following SAEs **do not** require reporting to SCTU using the Serious Adverse Event Report Form – Non-CTIMP:

- Prolonged hospital stay due to treatment of appendicitis

- Re-admission to hospital for complication of either treatment and/or appendicitis
- Admission to hospital for treatment of recurrent appendicitis
- Hospitalisations for elective treatment of a pre-existing condition

These events should be reported on eCRF as AEs.

6.3 CAUSALITY

A complete assessment of the causality must always be assessed by a medically qualified doctor who is registered on the delegation of responsibility log; this is usually the investigator.

If any doubt about the causality exists the local investigator should inform the SCTU who will notify the Chief Investigator. Other clinicians may be asked for advice in these cases.

Relationship	Description
Unrelated	There is no evidence of any causal relationship
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the study treatment). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possibly	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the study treatment). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
Probably	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Definitely	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

In the case of discrepant views on causality between the Investigator and others, SCTU will classify the event as per the worst case classification I and where applicable the Ethics Committee will be informed of both opinions within the required timelines.

6.4 EXPECTEDNESS

Expectedness assessments are made against the list of expected events below:

6.4.1 Expected Adverse Events:

A. Related to both treatment groups:
   (i) Abdominal pain or recurrent abdominal pain post treatment
   (ii) Fever
   (iii) Vomiting
   (iv) Diarrhoea/loose stool
B. Related to operative management:
   (i) Intra-operative damage to surrounding anatomical structures including but not limited to bowel loops, urethra, vessels, Fallopian tubes, ovaries
   (ii) Intra-operative finding of perforated appendicitis

(iii) Intra-operative bleeding requiring blood transfusion
(iv) Post-operative small bowel adhesions
(v) Post-operative intestinal obstruction
(vi) Post-operative hypertrophic scar (cheloid)
(vii) Intra-abdominal or pelvic abscess formation
(viii) Surgical Site Infection
(ix) Wound Infection or Dehiscence
(x) Recurrent abdominal pain

C. Related to non-operative management:
(i) Adverse events related to antibiotic use as per product monographs
(ii) Non-response to non-operative management (requiring appendicectomy)
(iii) Recurrent abdominal pain
(iv) Recurrent appendicitis

The nature or severity of should be considered when making the assessment of expectedness. If these factors are not consistent with the current information available then the AE should be recorded as 'unexpected'.

6.5 REPORTING PROCEDURES

All Adverse Events are to be recorded in the participant's medical notes. AEs should be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

Depending on the nature of the event, the appropriate reporting procedures below should be followed. A flowchart will be provided to aid in the reporting procedures.

6.5.1 Reporting Details

A SAE for Non-CTIMPs Form should be completed for all SAEs and faxed to SCTU within 24 hours of site becoming aware of the event.

Complete the SAE form and fax or email a scanned copy of the form with as many details as possible to the SCTU together with anonymised relevant treatment forms and investigation reports.

Or
Contact the SCTU by phone for advice and then fax or email a scanned copy of the completed SAE form.

SAE REPORTING CONTACT DETAILS

Please email or fax a copy of the SAE form to
SCTU within 24 hours of becoming aware of the event

Fax: 0844 774 0621 or Email: ctu@soton.ac.uk

FAO: Quality and Regulatory Team

For further assistance: Tel: 023 8120 4138 (Mon to Fri 09:00 – 17:00)

Additional information should be provided as soon as possible if the event has not resolved at the time of reporting.

6.5.2 Follow Up and Post- study SAEs

The reporting requirement for SAEs affecting participants applies for all events occurring up to 6 months after initial hospital discharge.

All unresolved adverse events should be followed by the investigator until resolved, the participant is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each participant to report any subsequent event(s) that the participant, or the participant's general practitioner, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a participant has discontinued or terminated study participation that may reasonably be related to this study.

6.5.3 Non-serious AEs

All adverse events should be recorded in the relevant eCRF and submitted to SCTU.

6.5.4 Pre-existing Conditions

Medically significant pre-existing conditions (prior to informed consent) should not be reported as an AE unless the conditions worsens during the trial. The condition, however, must be reported on the Medical History eCRF. Any adverse events which occur after informed consent taken should be recorded on the AE eCRF as per safety reporting section.

6.5.5 Serious Adverse Events

All SAEs should be reported within 24 hours of the local site becoming aware of the event. The SAE Non-CTIMP Form asks for nature of event, date of onset, severity, corrective therapies given, outcome, causality (i.e. unrelated, unlikely, possible, probably, definitely) and expectedness. The responsible investigator should assign the causality and expectedness of the event with reference to the events listed in Section 6.4.1 . The event term should be in accordance with the latest version of MedDRA and grades given in accordance with the NCI CTCAE v4.03, Additional information should be provided as soon as possible if the event has not resolved at the time of reporting.

6.6 SCTU RESPONSIBILITIES FOR SAFETY REPORTING TO REC

SCTU is responsible for onward reporting of:

- Information about SAEs which are both related to the research procedures and are unexpected, to the REC within 15 days of the sponsor becoming aware of the event
- All safety information to the REC in the annual progress report

7 STATISTICS AND DATA ANALYSES

7.1 METHOD OF RANDOMISATION

Patients enrolled in the study will be randomised to groups (1:1 ratio), online allowing instant assignment to treatment group 24 hours per day. This service will be provided by

the Southampton Clinical Trials Unit with telephone back-up. Minimisation will be used to ensure similarity between the groups in factors that may affect diagnostic accuracy and outcome of treatment.

7.2 SAMPLE SIZE

We will recruit participants from 3 centres for 12 months. Each centre treats 80-100 children per year with acute appendicitis of which we estimate at least 130 will be eligible. Assuming 40-50% will be recruited (i.e. 52-65 participants in our feasibility RCT) we will be able to estimate a true 40% recruitment rate with a 95% confidence interval (CI) of 31% to 49% and a true 50% recruitment rate with a 95% CI of 41% to 59%. We estimate 52-65 participants in our feasibility RCT which will be adequate to test treatment pathway procedures, data collection methods and loss to follow-up.

For our embedded qualitative work related to recruitment, we will recruit until we reach data saturation which we estimate will include analysing approximately 40 recruitment consultations, and interviewing 20-30 families, and 20-25 surgeons and other healthcare professionals.

7.3 INTERIM ANALYSIS

No interim analyses are planned.

7.4 STATISTICAL ANALYSIS PLAN (SAP)

CLINICAL TRIAL DATA ANALYSIS

Data analysis will be performed by the study statistician who will be blinded to treatment allocation by the use of coded data. As this is a feasibility study, all analyses will be treated as preliminary and exploratory and will be mainly descriptive. Feasibility outcomes (number of eligible patients, recruitment and retention rates, reasons for non-participation, success of blinding), treatment outcomes and complications will be presented by simple summary statistics with 95% confidence intervals.

Clinical outcome measures will be compared between treatment groups in an exploratory analysis, and variability estimates will be used to inform the sample size for a future definitive trial. The study will be reported in accordance with the CONSORT 2010 statement.

ANALYSIS OF DATA ARISING FROM EMBEDDED QUALITATIVE STUDY

Consultations and interviews will be digitally audio-recorded and then uploaded for transcription by a professional transcription service via a secure system. Transcripts will be pseudoanonymised before analysis by removing details such as person and place names and replacing these with codes.

Analysis of recruitment consultation data

We will analyse the recruitment consultations, by listening to these as well as working with the transcripts, documenting the interaction between recruiter and potential participant and exploring information provision, communication techniques, intervention preferences, and trial participation decisions. If analyses of the audio-recordings suggest that recruitment difficulties are potentially linked to communication during the recruitment consultation, this will be documented, fed back to the local PIs and training implemented. This may include simply providing feedback to the recruiter on altering particular words used to describe the trial/interventions or may include suggestions on how to make the consultation more balanced in terms of information given on the different interventions. It may also involve feedback to explore families' preferences for the interventions. We will

also assess the equipoise and views of surgeons recruiting to the trial, and investigate key ways in which their views differ from non-participating surgeons.

Analysis of recruitment consultations will use content analytic methods to describe in a structured manner what was said by whom and how often in the audio-recordings of recruitment sessions. More flexible constant comparison methods will be used to identify common or divergent themes, particularly focusing on the impact of statements by the recruiter on parent responses and views. Thematic analysis will be used to focus in great detail on certain sections of the transcripts, for example, in the interactions during which randomisation is offered. We will document the percentage recruited of those eligible using screening logs. Families who decline randomisation or do not accept their randomisation allocation will be noted. We will link these findings with qualitative data from the interviews where patients discuss the acceptability of trial methodology to determine the feasibility and acceptability of a full trial.

Analysis of interview data

We will analyse interview data for evidence of the needs, priorities and goals of families in relation to recruitment, randomisation, intervention preferences, their experiences and acceptability of the intervention and views regarding which outcomes are important. Analysis of interviews with surgeons and nurses at study sites will focus on their perceptions and experiences of recruitment, as well as their perceptions of the interventions and which outcomes are important. Analysis of interviews and focus groups with UK paediatric surgeons at non study sites will focus on perceptions of the interventions and other influences on their willingness to recruit patients to a future RCT, as well as their views on the design of such a trial.

Analysis of all interview data will draw on the principles of the constant comparative method and thematic analysis. One member of the research team will lead a process of 'cycling' between the developing analysis and new data. Other members of the qualitative study team (including at least one surgeon) will develop and test the analysis by periodic discussion and independent analyses of a proportion of transcripts to compare coding and findings.

Initially, each transcript will be read several times by the lead analyst, before developing open codes to describe each relevant unit of meaning, although coding will occur at multiple levels, from detailed descriptions of communication and experiences of the trial, to the general orientation of participants towards clinical research. Through comparison within and across the transcripts, the open codes will be developed into categories to reflect and test the developing analysis.

The categories will be organised into a framework to code and index the transcripts using QSR NVivo software. The framework categories will be continually checked and modified to ensure an adequate 'fit' with the data, whilst also accounting for variation in the data and 'deviant' cases. The categories and the assignment of data to them will be checked by a second member of the team. Our analytic approach will be informed by writings on quality in qualitative research [70].

We will not take participants' accounts only at face value, rather our approach will be interpretive and consider both latent and manifest aspects of the data (e.g. what we can learn from the way that participants talk as well as the explicit content).

HEALTH ECONOMICS ANALYSIS PLAN (HEAP)

A bottom-up micro-costing approach will be adopted to identify key cost drivers, which is characterised by the identification of patient-specific resource use and national tariffs as unit costs, and will be compared to the HRG tariff to identify the most appropriate costing method for the future definitive trial. In addition to secondary care, primary care and

patient born resource use will be identified. This will lead to the design of a modified version of the CSRI questionnaire. The Client Service Receipt Inventory (CSRI) is a research instrument developed to collect information of service utilisation and resource use patterns. One of the greatest strengths of this instrument is its adaptability. The finalised version of the CSRI will be piloted during the study and will be used in our future RCT. Descriptive statistics will be presented for costs, presenting the main cost drivers, and for QoL in QALY terms. At each occasion, inferences will be made as to the most appropriate way of measuring and collecting data for the economic analysis for application within the definitive trial. The feasibility and acceptability of data collection tools will be measured by completion rates and quality of data. The analysis of health economic data for this feasibility trial is focussed on enabling cost effectiveness analysis and cost utility analysis of our future RCT.

8 REGULATORY

8.1 CLINICAL TRIAL AUTHORISATION

This study is not considered to be a clinical trial of a medicinal product, so clinical trial authorisation from the UK Competent Authority the Medicines and Healthcare products Regulatory Agency (MHRA) is not applicable.

9 ETHICAL CONSIDERATIONS

The study will be conducted in accordance with the recommendations for physicians involved in research on human participants adopted by the 18th World Medical Assembly, Helsinki 1964 as revised and recognised by governing laws and EU Directives. Each participant's consent to participate in the study should be obtained after a full explanation has been given of treatment options, including the conventional and generally accepted methods of treatment. The right of the participant to refuse to participate in the study without giving reasons must be respected.

After the participant has entered the study, the clinician may give alternative treatment to that specified in the protocol, at any stage, if they feel it to be in the best interest of the participant. However, reasons for doing so should be recorded and the participant will remain within the study for the purpose of follow-up and data analysis according to the treatment option to which they have been allocated. Similarly, the participant remains free to withdraw at any time from protocol treatment and study follow-up without giving reasons and without prejudicing their further treatment.

9.1 SPECIFIC ETHICAL CONSIDERATIONS

1. Participants will be randomised to a novel care pathway.
   Although antibiotic treatment has not undergone rigorous evaluation for efficacy and safety, the existing literature supports the concept that non-operative treatment of acute uncomplicated appendicitis in children is safe [1-6]. Families will be fully informed that the clinical outcomes of this pathway are being investigated as part of this study, are of unproven efficacy but are considered safe.

   Regular clinical review will enable early identification of such patients, thereby minimising risk of complications or harm and minimising the adverse effects of unsuccessful treatment. Some patients/parents may be concerned that delay in appendicectomy may increase the rate of perforation and adverse events. However this is not borne out by the literature on large numbers of adult patients [7, 8, 76, 77] and participants will be counselled accordingly. The safety of participants will be further enhanced by the formation of the DMSC as outlined above.

In addition, children in the non-operative treatment group will continue to be at theoretical risk of recurrence of appendicitis. Whilst the risk of recurrence is low, the child and their families will be fully informed of this risk. We will seek permission from these families to hold their personal details in a secured registry and to contact them in the future to determine if they have had a recurrence.

2. Enrolment of children
   The main study will only enrol children. Informed consent will be taken from the child's parents with the child's assent if appropriate. The investigators all have experience of recruiting children for research studies including randomised studies and those involving a complex intervention. Consent will be taken by professionals who have received appropriate training in taking research consent from children and their parents.

3. Short timeframe within which participants will be asked to decide whether to participate.
   We are sensitive to the need for participants and families to be given adequate time to consider the study yet there is also a need for a decision to be made within a short period of time. Whilst appendicectomy is not typically a true surgical emergency it is considered an urgent procedure. The consent process is therefore 'time-constrained' rather than truly emergent. Participants will be made aware of this and consent will be obtained within a maximum of 4 hours of first discussion of the study. The research process will never impede on provision of safe and effective patient care.

9.2 ETHICAL APPROVAL

The study protocol has received the favourable opinion of a Research Ethics Committee or Institutional Review Board (IRB) in the approved national participating countries.

9.3 INFORMED CONSENT PROCESS

Informed consent is a process that is initiated prior to an individual agreeing to participate in a study and continues throughout the individual's participation. In obtaining and documenting informed consent, the investigator should comply with applicable regulatory requirements and should adhere to the principles of GCP.

Discussion of objectives, risks and inconveniences of the study and the conditions under which it is to be conducted are to be provided to the participant by appropriately delegated staff with knowledge in obtaining informed consent with reference to the patient information leaflet. This information will emphasise that participation in the trial is voluntary and that the participant may withdraw from the trial at any time and for any reason. The participant will be given the opportunity to ask any questions that may arise and provided the opportunity to discuss the study with family members, friend or an independent healthcare professional outside of the research team and time to consider the information prior to agreeing to participate.

9.4 CONFIDENTIALITY

SCTU will preserve the confidentiality of participants taking part in the study. The investigator must ensure that participant's anonymity will be maintained and that their identities are protected from unauthorised parties. On CRFs participants will not be identified by their names, but by an identification code.

10 SPONSOR

SCTU, Chief Investigator and other appropriate organisations have been delegated specific duties by the Sponsor and this is documented in the trial task allocation matrix.

The duties assigned to the study sites (NHS Trusts or others taking part in this study) are detailed in the Non-Commercial Agreement.

10.1 INDEMNITY

For NHS sponsored research HSG (96) 48 reference no.2 applies. If there is negligent harm during the clinical study when the NHS body owes a duty of care to the person harmed, NHS Indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the study. NHS Indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm. Ex-gratia payments may be considered in the case of a claim.

10.2 FUNDING

NETSCC HTA are funding this study.

Site payments

The payments assigned to the study sites (NHS Trusts or others taking part in this study) are detailed in the Non-Commercial Agreement.

This study is adopted onto the NIHR portfolio. This enables Trusts to apply to their comprehensive local research network for service support costs, if required

Participant payments

Participants will not be paid for participation in this study.

10.3 AUDITS AND INSPECTIONS

The study may be participant to inspection and audit by UHS (under their remit as Sponsor), SCTU (as the Sponsor's delegate) and other regulatory bodies to ensure adherence to the principles of GCP, Research Governance Framework for Health and Social Care, applicable contracts/agreements and national regulations.

11 STUDY OVERSIGHT GROUPS

The day-to-day management of the study will be co-ordinated through the SCTU and oversight will be maintained by the Study Management Group, the Trial Steering Committee and the Data Monitoring and Ethics Committee.

11.1 STUDY MANAGEMENT GROUP (SMG)

The SMG is responsible for overseeing progress of the study, including the trial, the Qualitative subgroup and survey and COS subgroup. The Chair of the SMG will be the Chief Investigator of the study.

The Qualitative Subgroup will meet every 2 months to input to these work streams and for quality assurance. They will report on progress back to the SMG following each meeting.

The survey work and the COS development subgroup will meet every 2 months and report back to the SMG after each meeting.

The CONTRACT SMG charter defines the membership, terms of reference, roles, responsibilities, authority, decision-making and relationships of the SMG, including the timing of meetings, frequency and format of meetings and relationships with other trial committees.

11.2 TRIAL STEERING COMMITTEE (TSC)

The TSC acts as the oversight body on behalf of the Sponsor and Funder. The TSC will meet prior to recruitment into the trial and every 3 months during the recruitment period to the clinical trial. The TSC will oversee the conduct of the clinical trial and review any substantial issues regarding the trial. In the event of any patient safety concern raised by the DMSC, the TSC will advise the SMG and the Sponsor on the continuation of the trial. The TSC will determine any rules for recommending that recruitment into the trial cease on the basis of patient safety or ethical concerns at their initial meeting. Membership of the TSC shall comprise an independent (to the study and any of the participating institutions) chair who will be a surgeon, 2 further independent members (one paediatric surgeon and one paediatrician) and a PPI representative.

The CONTRACT TSC charter defines the membership, terms of reference, roles, responsibilities, authority, decision-making and relationships of the TSC, including the timing of meetings, frequency and format of meetings and relationships with other trial committees.

11.3 DATA MONITORING AND SAFETY COMMITTEE (DMSC)

The clinical trial will have an independent Data Monitoring and Safety Committee (DMSC) whose primary function will be to monitor trial data for ethical or safety reasons. The DMSC will meet twice more on a planned basis (after 6 months recruitment to the clinical trial and at the end of the trial). Additional meetings will be convened as required or as directed by the TSC or CI. Any patient who 'fails' non-operative treatment within the trial and undergoes appendicectomy will be reported to the Trial Manager (TM) within 48 hours of appendicectomy. The TM will inform the TSC chairperson and will pass the clinical data relating to this patient to them. The TSC chair will hold responsibility for determining whether to ask the DMSC to meet and review the data from that patient. The DMSC will subsequently advise the TSC on their findings including an assessment of whether it is acceptable to continue to recruit patients. Membership of the DMSC will comprise a chair and at least 2 further members with the necessary clinical expertise, all of whom will be independent to the trial.

12 DATA MANAGEMENT

Participant data will be entered remotely at site and retained in accordance with the Data Protection Act (1988). The PI is responsible for ensuring the accuracy, completeness, and timeliness of the data entered.

The participant data is pseudo anonymised by assigning each participant a participant identifier code which is used to identify the participant during the study and for any participant- specific clarification between SCTU and site. The site retains a participant identification code list which is only available to site staff.

The Informed Consent Form will specify the participant data to be collected and how it will be managed or might be shared; including handling of all Patient Identifiable Data (PID) and sensitive PID adhering to relevant data protection law.

Trained personnel with specific roles assigned will be granted access to the electronic case report forms (eCRF). eCRF completion guidelines will be provided to the investigator sites to aid data entry of participant information.

Only the Investigator and personnel authorised by them should enter or change data in the eCRFs. When requested, laboratory data must be transcribed, with all investigator observations entered into the eCRF. The original laboratory reports must be retained by the Investigator for future reference.

A Data Management Plan (DMP) providing full details of the study specific data management strategy for the trial will be available and a Trial Schedule with planned and actual milestones, CRF tracking and central monitoring for active trial management created.

Data queries will either be automatically generated within the eCRF, or manually raised by the study team, if required. All alterations made to the eCRF will be visible via an audit trail which provides the identity of the person who made the change, plus the date and time.

At the end of the study after all queries have been resolved and the database frozen, the PI will confirm the data integrity by electronically signing all the eCRFs. The eCRFs will be archived according to SCTU policy and a PDF copy including all clinical and Meta data returned to the PI for each participant.

Data may be requested from the Data Access Committee at SCTU. Request will be considered on a monthly basis.

13 MONITORING

13.1 CENTRAL MONITORING

Data stored at SCTU will be checked for missing or unusual values (range checks) and checked for consistency within participants over time. Any suspect data will be returned to the site in the form of data queries. Data query forms will be produced at SCTU from the trial database and sent either electronically or through the post to a named individual (as listed on the site delegation log). Sites will respond the queries providing an explanation/resolution to the discrepancies and return the data query forms to SCTU. The forms will then be filed along with the appropriate CRFs and the appropriate corrections made on the database. There are a number of monitoring features in place at SCTU to ensure reliability and validity of the trial data, which are detailed in the trial monitoring plan.

The DMSC also have responsibility for specific central monitoring activities, as described in protocol section 11.3.

13.2 CLINICAL SITE MONITORING

There may be monitoring visits as and when required.

Source Data Verification

On receipt of a written request from SCTU, the PI will allow the SCTU direct access to relevant source documentation for verification of data entered onto the eCRF (taking into account data protection regulations). Access should also be given to study staff and departments (e.g. pharmacy).

The participants' medical records and other relevant data may also be reviewed by appropriate qualified personnel independent from the SCTU appointed to audit the study, including representatives of the Competent Authority. Details will remain confidential and participants' names will not be recorded outside the study site.

13.3 SOURCE DATA

Source documents are where data are first recorded, and from which participants' CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

14 RECORD RETENTION AND ARCHIVING

Study documents will be retained in a secure location during and after the trial has finished.

The PI or delegate must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. After study closure the PI will maintain all source documents and study related documents. All source documents will be retained for a period of 10 years following the end of the study.

Sites are responsible for archiving the ISF and participants' medical records.

The Sponsor is responsible for archiving the TMF and other relevant documentation.

15 PUBLICATION POLICY

Data from all centres will be analysed together and published as soon as possible.

Individual investigators may not publish data concerning their patients that are directly relevant to questions posed by the trial until the Study Management Group (SMG} has published its report. The SMG will form the basis of the Writing Committee and advise on the nature of publications. All publications shall include a list of investigators, and if there are named authors, these should include the Chief Investigator, Co-Investigators, Trial Manager, and Statistician(s) involved in the trial. Named authors will be agreed by the CI and Director of SCTU. If there are no named authors then a 'writing committee' will be identified.

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17 APPENDICES

Appendix A : Development of a Core Outcome Set

We will develop a core outcome set for the treatment of children with acute uncomplicated appendicitis using the Delphi survey consensus technique. The Delphi survey will be hosted within an online portal and infrastructure designed by the COMET Initiative, University of Liverpool (COMET DelphiManager). Participants will be asked to register, provide demographic details, and commit to all three rounds. Each participant will be allocated a unique identifier to anonymise participant responses, provide a means to send completion reminders and track responses through each round of the Delphi survey. Participants will be able to complete a paper version of the survey upon request. Participants will be from one of three stakeholder groups: (1) UK based consultant paediatric surgeons (identified from the BAPS membership list); (2) children (>10 yrs but <16 yrs) who have had acute appendicitis (identified from participating centres and who may or may not have been approached regarding CONTRACT); (3) parents of children (<16yrs) who have had acute appendicitis (identified from participating centres and who may or may not have been approached regarding CONTRACT). We aim to include at least 40 Paediatric Surgeons and at least 80 children/parents in the Delphi process. We will also involve children and parents in all stages of the Delphi process rather than incorporating their views only at final stages [48, 64]. We believe that this novel aspect is important as uptake of any future non-operative treatment of children will depend on providing accurate information about outcomes that are of most importance to children and parents.

Delphi round 1

In the first round the participant's name and email address will be recorded, eligibility confirmed for the relevant stakeholder group (surgeon, children, parent) and consent sought for the 3 round Delphi process. Three differently worded versions of the questionnaires with background information will be available for all rounds, as appropriate for each stakeholder group (surgeons, children, parents) using language identified in the qualitative interviews and agreed by the SSAG. Participants will be asked to complete each round of the Delphi exercise within 3 weeks and will be sent a reminder after 2 weeks. Surgeon stakeholders will be asked the key question 'What outcomes would influence whether you would treat children with uncomplicated acute appendicitis with non-operative treatment (antibiotics) or with appendicectomy?' The key question to be posed to other stakeholder groups will be similar but the wording will be altered based on our qualitative interviews and by the SSAG. Participants will be provided with a list of outcomes to be scored which will be derived from those identified in our recent systematic review [53] and any additional outcomes identified during qualitative interviews with families, surgeons, and other clinical staff. There will be an option for participants to add additional outcomes. The language used to describe each outcome will be defined by the SSAG with input from the qualitative interviews. Each participant will be asked to provide a score for each outcome (including those they have added themselves) using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) scale. The scale will be presented in the format 1 to 9, with 1 to 3 labelled 'not important', 4 to 6 labelled 'important but not critical' and 7 to 9 labelled 'critical' [65]. Stakeholder appropriate labels will be used for non-surgeon stakeholder groups as define by the SSAG.

Analysis of round 1

The response rate to round 1 will be determined for each stakeholder group. Additional outcomes provided by participants will be reviewed by two members of the COS team to ensure they represent new outcomes and included so long as they were proposed by at least 2 participants. If there is uncertainty then the Study Management Group will be consulted. For

each outcome, the number of participants who have scored the outcome and the distribution of scores (as a percentage who have scored each outcome) will be summarised by stakeholder group. All outcomes will be carried forward to round 2.

Delphi round 2

Only participants who have completed round 1 will be invited to participate in round 2. Each participant will be presented with their own score and the distribution of scores for each outcome from their own stakeholder group in round 1. Participants will asked to consider responses from the other members of their stakeholder group, and asked to re-score the outcome. Participants will also be asked to score any new outcome which was identified in round 1. Finally participants will also be asked whether each outcome should be included in a COS.

Analysis of round 2

The total number of participants invited to take part in round 2 will be recorded and response rate for each outcome recorded. Analysis of scores for round 2 will be identical to that for round 1. All outcomes from round 2 will be carried forward to round 3.

Delphi round 3

Only participants who have completed both rounds 1 and 2 will be invited to participate in round 3. In round 3 participants will be shown their own score and the distribution of scores, for each outcome, for their own stakeholder group and separately for each other stakeholder group. This novel approach will allow surgeons to take into account the views of children and parent stakeholders and vice-versa [48]. Participants will be asked to rescore all outcomes again and state whether they should be included in a COS. Finally, participants will be asked to identify the one single outcome which they believe is the most important for informing their treatment choice, and if they cannot identify a single outcome, a combination of essential outcomes.

Analysis of round 3

The total number of participants invited to take part in round 3 and response rate will be reported by stakeholder group and for all respondents across all stakeholder groups. For each outcome, the number of participants who have scored the outcome and the distribution of scores will be summarised together with the number of participants who have scored the outcome in all rounds. Results of each stakeholder group response will be compared with the whole group response to identify convergent and divergent opinions between stakeholder groups which will be addressed in the final consensus meeting. Each outcome will be classified as 'consensus in', 'consensus out' or 'no consensus' using previously recommended criteria [48, 49]. This *a priori* definition of consensus will reduce the chance of researcher bias influencing the COS. From these data a preliminary COS will be generated.

Final consensus meeting

All participants who have completed all 3 rounds of the Delphi exercise will be invited to attend. Representatives from each stakeholder group will be required in order for the consensus meeting to be quorate. Attendees will be provided with an overview of the results of the Delphi exercise including presentation of each outcome scored, how it was scored by each stakeholder group and its consensus status. For those outcomes for which 'no consensus' was achieved across all stakeholder groups at the end of the Delphi exercise, and for those for which consensus was achieved in at least one but not all stakeholder groups, further discussion will take place following which attendees will be asked to score each outcome anonymously. The final consensus meeting will not have the power to alter the inclusion or exclusion of outcomes in a COS for which 'consensus in' or 'consensus out' status has been assigned based on the

combined stakeholder results in the final round of the Delphi exercise. From this final consensus meeting we will establish a COS for the intervention of non-operative treatment of children with acute appendicitis and identify the primary outcome for our future RCT.

APPENDIX B - ADDITIONAL DATA TO BE COLLECTED

- Markers of severity of illness at randomisation including CRP, total white cell count, neutrophil count, clinical findings and need for fluid resuscitation.
- Alvarado score at randomisation (note: this will NOT be used for diagnostic purposes but as a clinical descriptor)
- Operative procedure performed – laparoscopic/open
- Operative findings - clinical description of appearance of appendix and intra-abdominal pathology
- Time of procedure
- Time between randomisation and operation in surgery group
- Precise detail of the reason for surgery in the non-operative treatment group
- Time in hospital from randomisation
- Time to resolution of symptoms from randomisation
- Abscess formation (documented by ultrasound, requiring prolonged antibiotics or drainage)
- Wound infection requiring antibiotics
- Wound dehiscence
- Total antibiotic consumption related to appendicitis (in hospital and out-patient, during 6 month follow-up)
- Compliance with out-patient antibiotic use
- Total analgesia consumption (in-hospital)
- Adverse effects of antibiotics
- Total number of intravenous cannulae required for antibiotics/intravenous fluids
- Time away from daily activities following discharge (measured using a diary card)
- Histology findings of appendicectomy specimens
- Recurrent appendicitis (histological diagnosis) requiring appendicectomy during the initial 6 month follow-up phase of this study and subsequently to a maximum of 5 years following randomisation (outside this application)
- All interventions, together with time and resource use in hospital will be identified. Resource use of community health (visits to GP, nurse and hospital out-patient) and loss of societal resources (child's days off from school, parent's days off from work) will be recorded at follow-up visits.

SUMMARY OF SIGNIFICANT CHANGES TO THE PROTOCOL

Protocol date and version	**Summary of significant changes**