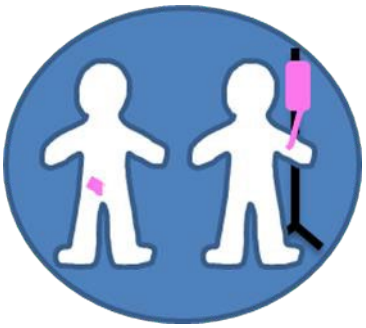
# CONTRACT 2



CONservative TReatment of Appendicitis in Children – a randomised controlled Trial – CONTRACT 2

**V8 – 30th October 2024**

**SPONSOR:** University Hospital Southampton NHS Foundation Trust
**COORDINATING CENTRE:** Southampton Clinical Trials Unit

| | |
|---|---|
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**Protocol authorised by:**

| | | | |
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| **Signature:** | | **Date:** | 18-Nov-2024 |
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## SPONSOR

University Hospital Southampton NHS Foundation Trust is the research sponsor for this study. For further information regarding sponsorship conditions, please contact the Director of Research and Development at:


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## FUNDER


This Trial is primarily funded by NIHR Health Technology Assessment programme, project number NIHR131346.


### Protocol Information

This protocol describes the [CONTRACT 2] Trial and provides information about procedures for entering participants. The protocol should not be used as a guide for the treatment of other non- Trial 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 Trial will adhere to the principles of Good Clinical Practice (GCP). It will be conducted in compliance with the protocol, the current Data Protection Regulations and all other regulatory requirements, as appropriate.

# Table of Contents

# 1 LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | Adverse Event |
| A&E | Accident and Emergency department |
| CEA | Cost Effectiveness Analysis |
| CHU-9D | Child Health Utility 9 Dimensions |
| COS | Core Outcome Set |
| eCRF | Electronic Case Report Form |
| CRP | C Reactive Protein |
| CRN | Clinical Research Network |
| CSRI | Client Service Receipt Inventory |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CUA | Cost Utility Analysis |
| DMEC | Data Monitoring and Ethics Committee |
| GCP | Good Clinical Practice |
| HE | Health Economics |
| HTA | Health Technology Assessment (NIHR) |
| HRQoL | Health Related Quality of Life |
| ISF | Investigator Site File |
| IV | Intravenous |
| ITT | Intention To Treat |
| 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 |
| QALY | Quality Adjusted Life Year |
| QoL | Quality of Life |
| RCT | Randomised Controlled 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 |

# 2 KEYWORDS

Appendicitis, appendicectomy, abdominal pain, core outcome set, randomised controlled trial, evidence based medicine, qualitative research ,economic evaluation

# 3 TRIAL SYNOPSIS

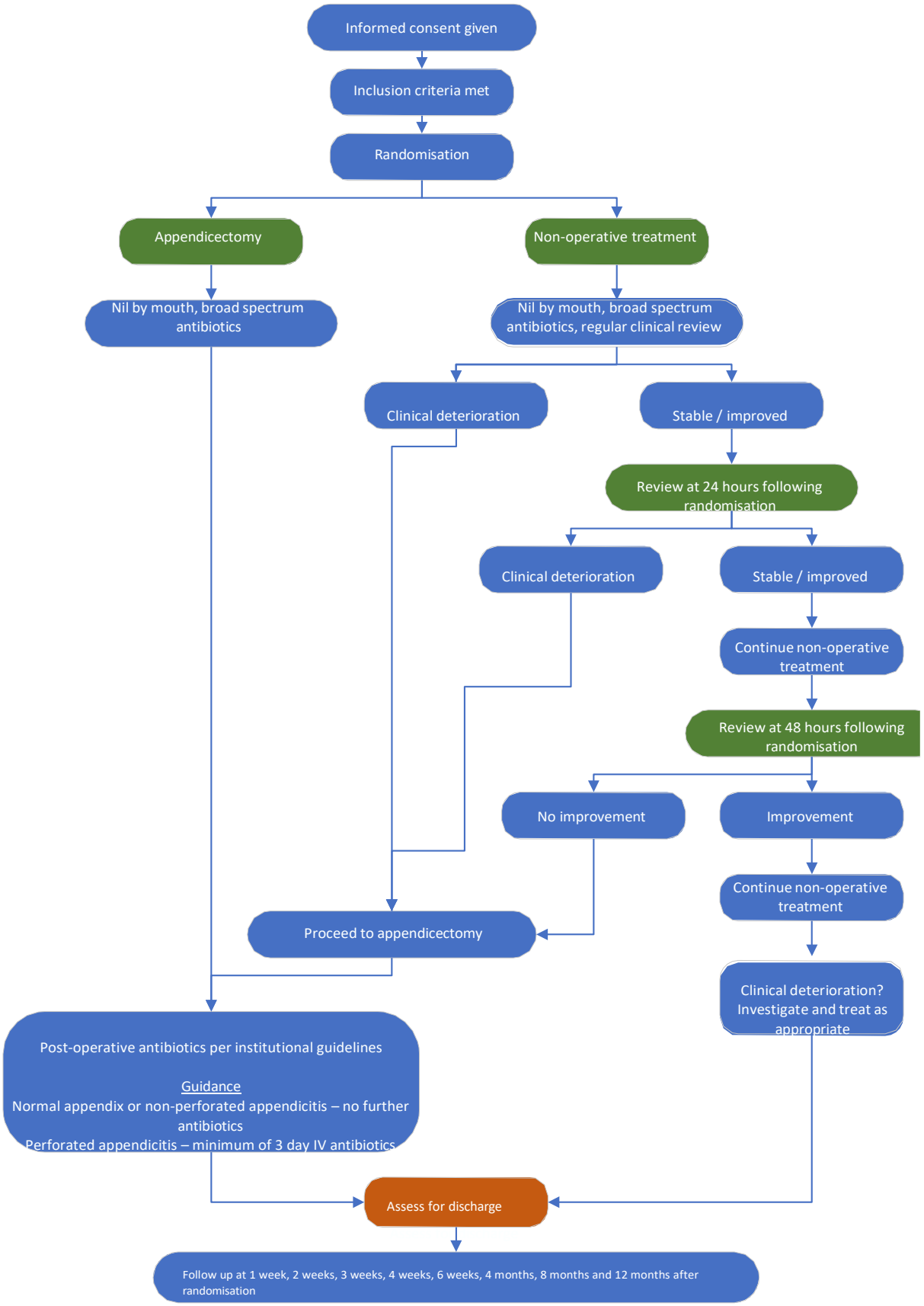
| | |
|---|---|
| **Short title/Acronym:** | CONTRACT 2 |
| **Full title:** | CONservative TReatment of Appendicitis in Children – a randomised controlled Trial |

| | |
|---|---|
| **Trial Phase:** | III |
| **Population:** | Children (aged 4-15 years) with a clinical diagnosis of acute uncomplicated appendicitis |
| **Primary Objective:** | To determine whether non-operative treatment is non-inferior to appendicectomy for the treatment of children with uncomplicated acute appendicitis |
| **Secondary Objectives:** | • to conduct a full economic evaluation of these treatments<br>• to compare duration of hosptial stay between arms<br>• to compare measures of recovery from acute appendicitis between arms<br>• to compare complications related to the underlying disease and treatment assigned<br>• to compare the need for further treatment between arms<br>• to compare persistent symptoms between arms<br>• to compare health care resource use between arms<br>• to compare quality of life and costs between arms |
| **Rationale:** | Currently, standard treatment is an appendicectomy. There is increasing interest and demand for non-operative treatment of appendicitis in children but a lack of data comparing non-operative treatment with appendicectomy. Comparative data are required to inform surgical practice. |
| **Trial Design:** | Randomised controlled trial with internal pilot. Children with uncomplicated acute appendicitis will be randomised to either 'appendicectomy' or a 'non-operative treatment' pathway that involves treatment with antibiotics and regular clinical review to ensure disease resolution. |
| **Sample size:** | We will test the hypothesis that non-operative treatment is non-inferior to appendicectomy. Based on the estimates of treatment success in each trial arm, a non-inferiority margin of 20% and anticipated loss-to-follow up rate of 15% we aim to recruit a total sample of 376 participants (188 per arm). Assumptions are based on 5% significance level and 90% power. |
| **Treatment/Intervention:** | A. Non-operative treatment pathway (broad-spectrum antibiotics and active observation)<br>B. Appendicectomy |

| | |
|---|---|
| **URL for Database:** | https://login.imedidata.com/login |
| **URL for Randomisation:** | https://prod.tenalea.net/ciru/DM/DELogin.aspx?refererPath=DEHome.aspx |

| | |
|---|---|
| **Primary Trial Endpoints:** | Treatment success |
| **Secondary Trial Endpoints:** | • duration of hospital stay<br>• measures of recovery from acute appendicitis<br>• complications<br>• need for further treatment<br>• persistent symptoms<br>• health care resource use<br>• quality of life and costs |
| **Total Number of Sites:** | Up to 50 NHS sites in the UK, of which up to 25 will be specialist NHS Paediatric Surgical Units and the remainder District General Hospitals. |

# 4 TRIAL SCHEMA



# 5 SCHEDULE OF OBSERVATIONS AND PROCEDURES

| **Visit / Time point (all measured from randomisation:** | **Baseline/ randomisation** | **Treatment** | **Discharge** | **1 week**[a] (+3 days) | **2 weeks**[a] (+3 days) | **3 weeks**[a] (+3 days) | **4 weeks**[a] (+3 days) | **6 weeks** (-1 wk / +2 wks) | **4 months**[a] (-1 wk / +2 wks) | **8 months**[a] (-1 wk / +2 wks) | **12 months**[a] (-1 wk / +2 wks) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Informed Consent | **X** | | | | | | | | | | |
| Eligibility evaluation | **X** | | | | | | | | | | |
| Medical History | **X** | | | | | | | | | | |
| Diagnostic Tests as per standard practice (blood test – Total WBC/CRP/Neutrophil, CT scan, Ultrasound) | **X** | | | | | | | | | | |
| Pregnancy Test[b] | **X** | | | | | | | | | | |
| Physical Exam (Abdomen exam) | | | | | | | | **X** | | | |
| Vital Signs (Temperature) | **X** | | | | | | | | | | |
| Randomisation | **X** | | | | | | | | | | |
| Appendicectomy (arm B only) | | **X** | | | | | | | | | |
| IV antibiotics (arm A only) | | **X** | | | | | | | | | |
| Doctor/Healthcare Professional Assessment | **X** | | | | | | | **X** | | | |
| Histology following surgery | | | | | | | | **X** | **X** | **X** | **X** |
| Discharge Assessment | | | **X** | | | | | | | | |
| Adverse Events | **X** | | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** |
| Health Economics – resource use | **X** | | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** |
| CHU-9D | **X** | | | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** |
| Patient data collected on app | | | | **X** | **X** | **X** | **X** | | | | |
| Client Service Receipt Inventory (CSRI) | | | | | | | | **X** | **X** | **X** | **X** |
| Recurrence | | | | | | | | **X** | **X** | **X** | **X** |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Complication requiring intervention under general anaesthesia | **x** | | | | | | | **x** | **x** | **x** | **x** |

[a] To be collected remotely via phone call and/or app
Data collected on app

- Pain relief taken Y/N
- CHU 9D proxy and self-report where appropriate
- Antibiotics taken Y/N
- Able to do normal daily activities Y/N
- Attended school Y/N
- Able to do full activities Y/N
- Parents missed work Y/N
- The last week have you had any contact with a health care professional(s) for your child's appendicitis? Y/N

[b] Only for those of childbearing potential

**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).

# 6 INTRODUCTION

## 6.1 BACKGROUND

Acute appendicitis is the commonest surgical emergency in children[36]. The lifetime risk is 7-8% with a peak incidence in the early teens. Appendicectomy is considered the gold standard treatment by most surgeons. In 2018-19 there were 8,439 emergency appendicectomies in England in children <16 years.

For parents the need for emergency surgery is frightening and many are keen to avoid surgery if an alternative is available. Surgeons are frequently asked "Does my child really need an operation?". Whilst appendicectomy is generally safe, it involves a general anaesthetic and an abdominal operation with inherent risks and potential complications. Work we have undertaken with parents shows that over 80% would be willing to consider nonoperative treatment for their child with appendicitis and 60% would prefer non-operative treatment to surgery if outcomes were similar (20% preferred surgery and 20% expressed no-preference).

An alternative would be to treat children non-operatively, without surgery but with antibiotics. This would have the benefit of avoiding an operation and potential side effects but would only be acceptable if antibiotic treatment has a high success rate and the risk of serious complications and recurrent appendicitis is low. Although research to date has confirmed that most children with uncomplicated acute appendicitis can be successfully treated without surgery, there have been no randomised controlled trials (RCTs) reported that directly compare these two very different treatments. Comparative data are needed to help inform future practice and in particular to inform treatment choices by children, parents, surgeons, doctors, healthcare professionals, NHS commissioners and healthcare policy makers.

Anticipating challenges in recruiting to such a RCT, we have already successfully performed an Health Technology Assessment (HTA) funded feasibility trial with embedded qualitative research and work to inform a health economic analysis[1-3] (CONTRACT feasibility study[4]). From this, we have confirmed that we can recruit participants to a RCT, gained valuable insights to optimise trial recruitment and retention, confirmed the safety of a non-operative treatment pathway in a UK setting and determined cost-drivers to underpin the design of a full economic analysis. We now plan to perform a large multicentre non-inferiority RCT, generating the evidence to inform future clinical practice in the UK.

The high incidence of appendicitis in children, its inherent demand for emergency in-patient treatment and surgery and the risk of complications have a clear and significant impact on children, their families and carers as well as economic impacts on the healthcare system and society. Through our contact with patients and families, and from qualitative research within our feasibility study, we have identified high demand for alternative non-operative treatment strategies. This is supported by the successful completion of the CONTRACT feasibility trial with a 50% recruitment rate, which was at the upper end of our target range.

Non-operative treatment has the potential to achieve clinical resolution of disease whilst removing the trauma of emergency surgery and potential complications. There is opportunity to reduce the impact and burden of treatment on children and their families. These include peri-operative complications (which occur in 5-15% of cases with significant complications in up to 7% [5,6,32,33]) and negative appendicectomy (i.e. normal appendix so an unnecessary operation) which occurs in approximately 10% of cases [9]. Signals from our feasibility trial suggest there may be further benefits to non-operative treatment in terms of more rapid recovery from appendicitis and a shorter duration of parental absence from work with non-operative treatment.

In addition to direct benefits to patients and families, we have shown there are likely significant cost benefits to non-operative treatment. A reduction in the need for emergency surgery, in particular, out-of-hours surgery (45% of appendicectomies are outside of normal working hours [10]), would have a cost benefit. Based on data from our feasibility RCT, we estimate that treatment of appendicitis without surgery would save

>£2000 per case (equivalent approximately to a 50% reduction in treatment cost). Earlier parental return to work may result in further cost savings at a societal level. Our proposed RCT includes a full health economic evaluation.

### 6.2 RATIONALE AND RISK BENEFITS FOR CURRENT TRIAL

Although acute appendicitis has been treated successfully without surgery in remote environments for some time [11], only in recent years has non-operative treatment been formally evaluated as primary therapy in developed healthcare systems. Whilst the current literature supports the safety and efficacy of non-operative treatment in children with uncomplicated appendicitis [12,13], there are a lack of data comparing outcomes of non-operative treatment with appendicectomy in children; just one small pilot RCT [14] has been reported which was inadequately powered for efficacy. It therefore remains uncertain as to whether non-operative treatment or appendicectomy offers the best outcomes for children. Despite evidence that non-operative treatment is acceptable to patients, our feasibility study demonstrated that UK surgeons rarely offer non-operative treatment [4]. Further, the majority of UK surgeons are at present unconvinced by the strength of the evidence for non-operative treatment as an alternative to appendicectomy but importantly, would be willing to participate in a RCT. Generating these comparative data are essential to inform evidence-based practise.

Of note, there are a few ongoing trials comparing non-operative treatment with appendicectomy elsewhere in the world. These include 3 RCTs (recruiting largely from North America [15], Australia [16] and the Netherlands) and 1 non-randomised (patient preference North American) trial. These trials remain either open to recruitment or in follow-up at the current time. Although these non-UK studies, when reported, may provide some further scientific evidence, results from other countries will not be directly applicable to the NHS.

Attitudes to appendicitis, treatment practice and outcomes from appendicectomy differ in the UK compared to other developed countries. For instance, diagnostic imaging is not routinely used in the UK, the take-up of laparoscopic appendicectomy was relatively slow compared to other countries with developed healthcare systems, very few surgeons in the UK treat any type of appendicitis without appendicectomy and the incidence of negative appendicectomy (i.e. the appendix is not inflamed on pathological examination) in the UK is high (10%) compared to other countries. Furthermore, the NHS represents a unique health economic environment and it is unlikely that any economic evaluation of non-operative treatment performed outside the UK will be meaningful within the NHS. The attitude of UK surgeons and the population to appendicitis make it imperative that this health technology be evaluated in the UK setting. Performing a UK study is essential to generate appropriate data for the UK population, to inform local healthcare choices within the NHS and importantly data that has the potential to change practice.

## 7 TRIAL OBJECTIVES

| | Objective | Endpoint used to evaluate |
|---|---|---|
| **Primary:** | To determine whether non-operative treatment is non-inferior to appendicectomy for the treatment of children with uncomplicated acute appendicitis. The primary outcome of 'treatment success' will be assessed at 1 year following randomisation. | Treatment success at 1 year (see definition below in 8.1.1) |
| **Secondary:** | To compare non-operative treatment with appendicectomy in terms of other important patient and family centred outcomes and cost. Outcomes will include duration of hospital stay, measures of recovery from acute appendicitis, complications, need for further treatment, persistent symptoms, health care resource use, quality of life and costs. We will measure all applicable outcomes in our recently developed core outcome set. | See table below in section 8.1.2 |

# 8 TRIAL DESIGN

A multicentre, open label randomised non-inferiority controlled trial with internal pilot and health economic evaluation 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. Patients enrolled in the study will be randomised at a ratio of 1:1.

## 8.1 TRIAL ENDPOINTS

### *8.1.1 Primary endpoint*

Treatment success, to be measured at 1 year following randomisation and defined as recovery from acute appendicitis and having none of the following: negative appendicectomy, complication requiring intervention under general anaesthesia, failure of non-operative treatment during initial hospital admission (treated with appendicectomy), recurrent appendicitis.

### *8.1.2 Secondary endpoints*

| Outcome | Timing of measurement | Method of measurement |
|---|---|---|
| Negative appendicectomy*$ | Hospital discharge, 6wk | Research nurse |
| Intra-abdominal abscess* | Hospital discharge, 6wk | Research nurse |
| Complication requiring intervention under general anaesthesia | Hospital discharge, 6wk, 4, 8, 12 months | Research nurse |
| Bowel obstruction* | Hospital discharge, 6wk, 4, 8, 12 months | Research nurse |
| Wound infection* | Hospital discharge, 6 week review | Research nurse |
| Other wound complication* | Hospital discharge, 6 week review | Research nurse |
| Antibiotic failure*$ | Hospital discharge, 6 week review | Research nurse |
| Length of hospital stay* | Hospital discharge, 6wk, 4, 8, 12 months | Research nurse |
| Histology of appendix | 6wk, 4, 8, 12 months | Research nurse |
| Adverse events* | Hospital discharge, 6wk, 4, 8, 12 months | Research nurse |
| Recurrent appendicitis*$+ | 6 week and 4, 8, 12 months | Research nurse |
| Readmission to hospital* | 6 week and 4, 8, 12 months | Research nurse |
| Appendicectomy without recurrent appendicitis on histology | 6 week and 4, 8, 12 months | Research nurse |
| Patient's quality of life* (CHU-9D) | 1, 2, 3, 4, 6 weeks and 4, 8, 12 months | Smartphone app and Research nurse |
| Healthcare resource use (shortened CSRI) | 6 week and 4, 8, 12 months | Research nurse |
| Death* | Hospital discharge, 6wk, 4, 8, 12 months | Research nurse |
| Was pain relief taken? Y/N | Daily for 3 weeks following discharge | Smartphone app |
| Able to do normal daily activities Y/N | Daily for 3 weeks following discharge | Smartphone app |
| Attended school Y/N | Daily for 3 weeks following discharge | Smartphone app |
| Able to do full activities* Y/N | Daily for 3 weeks following discharge | Smartphone app |
| Parents missed work Y/N | Hospital Discharge, daily for 3 weeks following discharge | Research Nurse and Smartphone app |

*Indicates outcome within core outcome set;

$ indicates part of composite primary outcome

[+]Recurrent appendicitis is defined as symptom recurrence followed by EITHER appendicectomy with histological confirmation of acute appendictis OR a Doctor/Surgeon diagnosis of appendicitis with appendix mass or abscess treated non-operatively; appendicectomy without histological confirmation of acute appendicitis is a separate secondary outcome.

# 9 DEFINITION OF END OF TRIAL

The study will end once the final participant recruited has completed the 12 month follow up period and this data has been entered onto the trial database.

# 10 SELECTION AND ENROLMENT OF PARTICIPANTS

For the duration of the trial at sites, the Chief Investigator is able to provide ongoing support through recruitment training. This focuses on the recruitment aspect and ensuring that equipoise is maintained whilst recruiting patients. The aim of this is to ensure recruitment is optimised at each site and ensure new staff who join the CONTRACT 2 team are appropriately trained on the study. This training will be available to sites at any time it is deemed appropriate and will be offered routinely approximately every 6 months that a site has been open.

## 10.1 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 staff since our preparatory work, with the National Institute of Health Research Clinical Research Network (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 anyone other than surgeons 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 other research staff . Recruitment capacity will therefore be available 16 hrs per day. This provides a realistic approach for a multicentre trial.

Parents will be approached by a member of the surgical team and a research nurse or other research staff (when available), who will explain the study to them and invite them to participate. The CONTRACT 2 study will be explained to parents and children with the aid of age specific information sheets and a short video presentation. The patient video will also be made available via a web link to allow parents or guardians, who cannot be in hospital with their children at the time of recruitment, to access the same trial information as the consenting parent or guardian.

Written consent for inclusion in the clinical trial will be obtained from all families. Assent (as opposed to consent) may be obtained from children aged 8 years or older who wish to give it (as suggested by our pre-study PPI work with young people). Consent for CONTRACT 2 will be sought only after a full explanation of the study has been given and an information leaflet offered. Consent for the CONTRACT 2 study can be obtained by a member of the surgical team or a qualified and delegated member of the research team if they have been part of the initial discussion, however the initial discussion regarding study participation should occur with a member of the surgical team.

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 we will aim to obtain consent within 4 hours of first discussion of the study. To allow for parents to consider their participation in

the study for longer and when circumstances permit (for example when the study is first discussed with parents in the evening or overnight, and it is acceptable and appropriate to delay making a decision until the next morning) the absolute maximum time between first discussing the study and obtaining consent will be 18 hours. 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 meetings held at a convenient time at or near each centre (or delivered remotely via videoconference) to which all members of the clinical team will be invited (core and specialist surgical trainees, research staff 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 Doctor/Surgeon remains free to give alternative treatment to that specified in the protocol at any stage if they feel 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.

Upon completion of the informed consent form, a copy will be given to the participant, a copy stored in the participant's medical notes and the original filed in the site trial file. A copy of the signed ICF and PIS will also be uploaded to participants' electronic medical record. A copy of the consent form should be sent via secure FTP UoS Safesend https://safesend.soton.ac.uk, to allow for central monitoring upon request.

We will not exclude participants on the basis of their previous or ongoing involvement in other research, unless obliged to do so by the relevant protocols of other research studies.

Once a child turns 16, some sites may be required by their local R&D department to re-consent the participant for ongoing data collection during the follow-up period. If this is required by local site R&D then verbal consent can be obtained by a member of the clinical or research team either in person or via telephone. This should be documented on a specific verbal consent form. This only needs to be done if the site based R&D require it, it is not requested to be done by the CONTRACT 2 Team.

### 10.2 INCLUSION CRITERIA (ALL OF THE FOLLOWING TO BE MET)

1. Children aged 4–15 years
2. Clinical diagnosis, with or without radiological assessment, of acute appendicitis which prior to study commencement would be treated with appendicectomy
3. Written informed parental or guardian consent, with child assent if appropriate

### 10.3 EXCLUSION CRITERIA (EXCLUDE IF ANY OF THE FOLLOWING ARE PRESENT)

4. Complicated appendicitis score (Table 1) of 4 or greater
5. Clinical or Radiological findings to suggest perforated appendicitis
6. Presentation with appendix mass
7. Previous episode of appendicitis or appendix mass treated non-operatively
8. Major anaesthetic risk precluding allocation to the appendicectomy arm
9. Documented allergy to first and second line broad spectrum antibiotics preventing allocation to non-operative treatment arm
10. Positive pregnancy test (only required for female patients of child bearing potential)

Table 1: Complicated appendicitis score

| Parameter | Points |
|---|---|

| | |
|---|---|
| **Rebound Tenderness** | 1 |
| **Duration of Pain ≥ 48 hours** | 1 |
| **Temperature* ≥ 37.5$^0$C** | 1 |
| **Neutrophil Count ≥ 11 (x10^9/L)** | 2 |
| **CRP ≥ 50 (mg/L)** | 2 |

*documented temperature, in hospital, at any stage prior to diagnosis

**Please note that test results and clinical findings used for this score should be those available at the time the diagnosis of appendicitis was made and the participant first approached about the trial**, and not earlier or later tests /clinical findings either at presentation or after enrolment in the trial. The results used to calculate the CAS above should be input to the eCRF as soon as possible in the Baseline Folder

## 11 SCREENING FAILURES

A member of the research team in each centre will complete a screening log capturing **all children** aged 4-15 admitted with appendicitis. Any potential participants approached will have their decision to participate in the CONTRACT 2 Study documented. All potential participtants will have their gender, age, intials and reason for screen failure if applicable recorded on the screening log.

The screening log will be discussed with the surgical team on a regular basis. Screening logs will be sent to the CTU Trial Manager (TM) on a monthly basis.

## 12 RANDOMISATION PROCEDURES

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

# 13 TRIAL OBSERVATIONS AND PROCEDURES

### 13.1 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 team at each centre to ensure the participant was eligible at the time of diagnosis.

Doctors/Surgeons 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 eCRF 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 Shera Score [37] will also be recorded as a clinical descriptor i.e. it will not be used for diagnostic purposes.

## 13.2 TRIAL PROCEDURES

***Randomisation to Discharge***
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 intravenous antibiotics (determined by local hospital standard antibiotics for appendicitis, as per our feasibility trial), analgesia and regular clinical review to detect symptoms and signs of significant clinical deterioration including, but not limited to, increasing fever, increasing tachycardia, and increasing pain/tenderness. In our feasibility trial we recommended a minimum period of being 'nil-by-mouth' but learnt from experience that this is unnecessary and deterred some children from participating, therefore this requirement has been removed for this protocol.

Children receiving non-operative treatment who, in the opinion of the consultant surgeon in charge of their care have clinically deteriorated such that immediate appendicectomy is mandated, will undergo appendicectomy at any stage. A formal review will be performed at 24 hours following randomisation and any child deemed to have significantly deteriorated (e.g. deterioration in objective clinical observations) will undergo appendicectomy. Those who are stable or clinically improving will continue with non-operative treatment. Those who are not showing clinical signs of improvement at 48 hours following randomisation will undergo appendicectomy. This decision 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. If at any time the child is stable and meets the criteria for discharge, they can be sent home without having to wait for the specified time points for clinical review, if this occurs, please ensure this is documented appropriately in the patient notes.

Children who require appendicectomy for failure of non-operative treatment will be treated post-operatively according to a standardised treatment regime already in use at participating institutions and identical to that to be used in children in the appendicectomy treatment group (see below). Children in whom non-operative treatment is successful will receive a minimum of 24 hours intravenous antibiotics and then be converted to oral antibiotics (co-amoxiclav as per standard practice) 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, adequate oral pain relief and be mobile. They will receive a total course of 10 days antibiotics following randomisation. Children who receive non-operative treatment will not be offered interval appendicectomy, but they and their parents will be counselled about the risk of recurrence using best available data. Children presenting with suspected recurrent appendicitis during the 1-year follow-up period will not be eligible for re-randomisation. These cases will be recorded and typically treated with appendicectomy and not treated non-operatively unless re-presentation is with appendix mass or abscess and non-operative treatment is felt preferable by the clinical team.

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 Doctor/Surgeon 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 and timing 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 urgent appendicectomy which is standard practice for children of all ages at all participating centres. The procedure may be performed by a suitably experienced trainee (as is routine current practice) or a consultant. The procedure may be performed open or laparoscopically at the discretion of the clinical team according to their current practice (in our feasibility trial just 1 of 35 urgent appendicectomies was performed open).

As per current routine practice, a peritoneal microbiology swab will be taken at the time the peritoneum is first opened and any peritoneal fluid sent for microbiological culture. Participants will receive intravenous antibiotics from the time of randomisation and be treated post-operatively with intravenous antibiotics according to defined and standardised treatment regime already in use at our institutions. Specifically, children with uncomplicated acute appendicitis or a macroscopically normal appendix will receive no further antibiotics. If, unexpectedly a perforated appendix is discovered at surgery (defined as a faecolith or faecal matter within the peritoneal cavity or visualisation of a hole in the appendix[17]) then intravenous antibiotics will be continued for a minimum of 3 days, with a minimum total course of antibiotics of 5 days (intravenous and oral). It is not possible to completely 'protocolise' the duration of antibiotic therapy due to anticipated variation in response to treatment.

The type of antibiotics initially used will be identical to those used in the non-operative treatment arm (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

***Discharge from hospital***

The decision to discharge the child home will be made by the clinical team using standard clinical criteria for both treatment arms which will be: afebrile, vital signs within normal limits, able to tolerate oral intake, able to mobilise. The time the decision to discharge was made and the time of actual discharge will be recorded.

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, instructions for downloading the smartphone app (a paper patient diary card can be supplied for those without access to a smartphone), a questionnaire booklet if applicable, 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 12 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 13 for more information regarding follow up.

The following data will be collected at discharge:

- Date / time of decision to discharge
- Date and time of first eating
- Adverse events
- Parental days work missed until discharge

***Internal Pilot Stage***

The pilot is to ensure that recruitment outside of the 3 sites used in our feasibility trial is possible, confirm our anticipated recruitment rate, implement recruiter training, and adjust the overall trial profile if necessary. We have devised a comprehensive program of recruiter training and re-training, using an evidence based approach with some limited qualitative work and informed by our feasibility study (CONTRACT 1), which we believe is crucial to achieving target recruitment.

We have focused pilot phase metrics on actual recruitment, which is dependent on initiating sites and successfully recruiting participants. In CONTRACT 1 we successfully opened all 3 sites on the same day. Whilst in CONTRACT 2 we will stagger site opening and aim to open all sites within the first 6 months of recruitment.

The decision of progression to full trial will be taken by the Trial Steering Committee (TSC) in conjunction with the funder, based on traffic light criteria assessed after 12 months recruitment:

- GREEN (immediate progression to full RCT): 100% of anticipated recruitment after 12 months recruitment.
- AMBER (prolongation of pilot phase for further 6 months to allow further identification of sites and/or further training at existing sites) 75 - 99% of anticipated recruitment.
- RED (undertake urgent detailed review of options with Trial Steering Committee and report to HTA) <75% anticipated recruitment.

| Pilot phase criteria | Red | Amber | Green |
|---|---|---|---|
| % Threshold (of participants) | <75 | 75-99% | 100% |
| Total number of participants recruited | <120 | 120-159 | ≥160 |
| Number of sites opened* | <7 | 7-9 | ≥10 |

### 13.3 EMBEDDED COMMUNICATION STUDY

A qualitative study was embedded in CONTRACT 2 (The CONTRACT 2 Communication Study) during the pilot phase to identify potential barriers to recruitment and improve informed consent. Our qualitative study embedded within CONTRACT found that while most surgeons approved of the research question being addressed by the trial, many preferred surgery to conservative treatment [4,18]. This preference was evident

from the concern's surgeons expressed about conservative treatment during qualitative interviews, and how surgeons presented the treatment arms to families in the early months of CONTRACT, which often communicated their preference for surgery. Presenting treatment arms in a balanced way without indicating a preference for one treatment over another is known to facilitate trial recruitment and consent [19, 20]. In CONTRACT, the qualitative team worked with surgeons to enhance communication about the trial by developing and delivering two bespoke trial communication training sessions across sites informed by ongoing analysis of audio-recorded CONTRACT consultations and interviews with families and health professionals. After each training session delivered, surgeons' presentation of treatment arms became more balanced and CONTRACT recruitment rose markedly.[4]

Building on learning from the CONTRACT Communication Study, the sub-study team developed and delivered bespoke communication training to optimise surgeons' communication about CONTRACT 2 and families' experiences of being approached about CONTRACT 2. This identified potential recruitment issues by monitoring CONTRACT 2 recruitment at all sites and requesting sites to audio-record CONTRACT 2 consultations. Researchers from the University of Liverpool reviewed CONTRACT 2 consultation recordings to inform bespoke trial communication training, which was provided to all sites on an ongoing basis during the internal pilot phase of CONTRACT 2.

The Communication Sub-Study has now completed and closed to recruitment (as of 29th February 2024).

***Method***

The CONTRACT 2 Communication Study team provided sites with audio-recording devices. During the internal pilot surgeons and research nurses (recruiters) routinely sought verbal permission to audio-record CONTRACT 2 consultations with families during which: CONTRACT 2 was discussed before consent was sought, consent was obtained, and the family was informed of their treatment allocations. Recruiters briefly outlined the purpose of audio-recording the consultation and recorded the consultations if permission was granted. At the end of the consultation or at the point of taking consent for CONTRACT 2, recruiters obtained written consent for the audio-recording to be uploaded to the CONTRACT 2 Communication Study team. If the family declined to provide written consent, the audio-recording was deleted from the device. If the family provided written consent and their CONTRACT 2 consultation was recorded, a member of staff from the site liaised with the CONTRACT 2 Communication Study researcher to upload the audio-recorded CONTRACT 2 consultation(s) via a secure encrypted system.

The consent forms and audio-recordings will be stored until the end of the CONTRACT 2 study and then destroyed as per UKDS recommendations (https://www.ukdataservice.ac.uk/manage-data/store/disposal). Although the audio devices were not encrypted, measures were taken to ensure the information remained secure. Sites were advised to keep the device in a locked drawer or secure place when not in use. The recordings were uploaded at the first opportunity, then once confirmation was received from Liverpool that the recording was received, the recording was then deleted from the device. Only patient initials were obtained on the recording along with the date, time and month/year of birth. A patient identifier code was applied to each audio file captured, no other identifiable information on the participant was captured on the audio-recordings. A member of staff also obtained written consent and completed a proforma that captured fields providing details of the consultation, such as the name of recruiter, date of the consultation, patient age, CONTRACT 2 participation status, and treatment allocation. The Communication Sub-study consent form, health care professional consent form and proforma were submitted to the CONTRACT 2 Communication Study team via the same encrypted system (or via end-to-end nhs.net email accounts) All data is stored on the University of Liverpool Active Datastore and is only be accessible to members of the CONTRACT 2 Communication Study team. The researcher, supervised by Professor Bridget Young, listened to and reviewed samples of CONTRACT 2 consultations to inform bespoke feedback for each site.

***Plan for bespoke training***

Before CONTRACT 2 recruitment started, the qualitative research team delivered an initial trial communication group training session to optimise surgeon and research nurse communication with families about CONTRACT 2. All recruiters who were involved in recruiting to CONTRACT 2 (at the time of trial opening) attended the event. This session was based on the successful QUINTET programme[19] but also incorporated key findings from the CONTRACT Communication Study [4,18]; training covered key themes, such as avoiding misinterpreted or misunderstood terms, exploring family treatment preferences, and highlighting families' frequently asked questions.

A package of resources and support materials was developed and disseminated after being informed by recruiter feedback from CONTRACT and in consultation with site staff, including a demonstration video that incorporates key learning points from CONTRACT and a hints and tips handout. The hints and tips handout was regularly updated and circulated during the pilot phase of CONTRACT 2, in response to ongoing review of the CONTRACT 2 consultations.

During the pilot phase of CONTRACT 2, the Communication Sub-Study team identified and offered additional support refresher training to sites that might benefit from it (e.g. those with lower approach/recruitment rates or those that have encountered challenges in discussing CONTRACT in a balanced way with families). This involved reviewing their CONTRACT 2 consultations and visiting such sites to support the team (or deliver training via video call if more appropriate) during months 3-9 of the pilot phase.

***Evaluating training***

In the CONTRACT Communication Study, we qualitatively and quantitatively evaluated the impact of communication training on trial communication and recruitment throughout the course of CONTRACT. The CONTRACT recruitment rate increased following each training session, but it increased more markedly after the second session of tailored training. In the end-of-study report, we identified that future work is needed to robustly evaluate the impact of communication training on trial recruitment and recruiter confidence[4].

In the CONTRACT 2 Communication study, attendees were asked to complete questionnaires before and after all training sessions. These questionnaires assessed their self confidence in approaching families about CONTRACT 2 and explored trial communication concepts, such as conveying equipoise and exploring family treatment preferences. Perceived impact of training and CONTRACT 2 recruitment rates were also assessed following the session. The qualitative research team input the results of the questionnaire data into the program SPSS and examined trends and correlations associated with the impact of training.

## 13.4 EMBEDDED HEALTH ECONOMIC STUDY

Data generated from our feasibility study [3] (CONTRACT) provided important insights designing the economic evaluation of the proposed intervention in this definitive RCT. The proposed economic evaluation builds upon evidence acquired from our previous work in terms of defining the timeline of assessment in relation to health outcomes, the most appropriate Health-related quality of life (HRQoL) instrument, as well as defining the most appropriate methods and data collection tools targeting the main costs associated with the intervention. The economic analysis of this study will be based on an assessment of the incremental cost per successfully treated child (primary outcome) and the incremental cost per Quality Adjusted Life Year (QALY) gained.

In our feasibility study following a detailed micro-costing approach we established the potential of economic savings for the NHS. Alongside this definitive RCT we will conduct a full economic evaluation assessing the cost-effectiveness of the proposed intervention as compared to standard care (appendicectomy). Therefore, the within trial economic analysis, adherent to guidelines for good economic evaluation practice[21, 22, 23], will include (i) a cost-effectiveness analysis (CEA) using the primary outcome at the end of the follow-up (1 year) and (ii) a cost-utility analysis (CUA) using HRQoL (CHU-9D) conducted at 6w to assess the short-term impact of the intervention in terms of QALYs.

The perspective of the economic study will be that of the NHS. All cost-effectiveness results will be presented on: (i) the cost-effectiveness plane, which captures the uncertainty around the results showing the incremental costs and incremental effects of the comparison of interest in a 2-dimentional plot, and (ii) the cost-effectiveness acceptability curves, which graphically represent the uncertainty in terms of probabilities, regarding the cost-effectiveness of the intervention. We will also report on the economic implications for the NHS of non-operative treatment. This will include developing and reporting a tariff for the non-operative treatment of uncomplicated acute appendicitis since this is not currently available within the NHS Reference Costs data.

**Data Collection and Health Economic outcomes**

Resource Use, Costs and HRQoL data: Guided by work done and cost drivers identified in our feasibility study[1] we will adopt a comprehensive approach collecting resource use data from hospital records, follow up phone calls with a research nurse and from parents using a smartphone app. Our results from the feasibility study clearly indicated that the main cost drivers in addition to treatment costs during admissions, were the A&E visits, the outpatient appointments and to a lesser extent the GP visits. Therefore, the data collection for this definitive RCT, in addition to hospital admissions (secondary care) data will include data for the main cost drivers collected from parents/carers. The experience acquired from the feasibility study was that completion rates were significantly lower providing poor data when the questionnaires were not completed by a research nurse. Therefore, we adjusted our data collection method to take this consideration into account. The primary care data from parents will be collected by research nurse phone calls and in person interviews using a short modified version of the CSRI[24, 25, 26] (Client Service Resource Inventory) questionnaire, the e-CSRI (electronic CSRI) questionnaire we modified and used in our feasibility study. For secondary care data we will use the Patient Level Information and Costing Systems (PLICS)[27] data for acute services records activity and cost information for admitted patient care, outpatient appointments and A&E attendances (collection of this data is detailed in appendix 1). The results from our feasibility study support the use of PLICS data as a reliable alternative to micro-costing. Unit cost will use the NHS Reference Costs [28] and Personal Social Services Research Unit [29] (PSSRU) data in addition to other unit costs as appropriate. To allow reporting in QALY terms, following findings from our feasibility study we will use the CHU-9D. The HE data in addition to assessing the cost-effectiveness of the proposed intervention will allow as to explore potential cost savings and to define the NHS tariff of treating appendicitis non-operatively.

Timing of Health Economic (HE) Data collection: The data collection refers to hospital records for admission(s) to hospital(s) up to 12m duration, including recurrences. Parents/guardians through the smartphone app will report any incidence of appendicitis or pain relevant to appendicitis that required medical attention and health care resource use, weekly for 4w . These records will be discussed in detail during the 6w visit. HE data will also be collected during phone call visits at 4m, 8m and 12m and the e-CSRI questionnaire will be completed by research nurse during these visits at 6w, 4m, 8m and 12m.
For QoL data, our previous work shows that timing is an important consideration collecting QoL data and estimating QALYs for this intervention. While there was a significant difference in QoL at 2w this difference was not present at 6w and both groups have had returned to almost full health. Therefore, we have added additional time collection points and the QoL data will be collected at baseline, weekly up to 4w and then at 6w, in order to identify the return to full health and normal life for children in both arms. The CUA will report this short-term outcomes in QALYs.

**Health Economic Analysis**
Overall the economic evaluation will report the long-term results from the CEA at 1y using the primary outcome, reporting cost per successfully treated child. The CUA will report the short to medium-term cost per QALY gained at 6w, when full recovery for both arms is expected. The reason we will report CUA at 6w is because if we extend the time to 1y this will dilute the actual difference between the two arms in QALY terms and it is important to show the short-term implication in QALY terms. However, sensitivity analysis will explore long-term implications by incorporating recurrence of appendicitis, both in terms of increased costs and reduced QALYS. The potential of bias will also be explored using sensitivity analysis if increased cross-

over between arms is observed. As part of the economic analysis we will also report the economic implications for the NHS in terms of defining tariff for the non-operative treatment option and reporting on the economic impact this might have to the NHS. A full Health Economics Analysis Plan will be developed.

# 14 FOLLOW UP

The following data will be collected daily for 3 weeks via smartphone app

- Was pain relief taken? Y/N
- Were antibotics taken? Y/N
- Able to do normal daily activities (Normal Activity: Sitting down, standing up, walking, running, brushing teeth/hair, showering, dressing, talking with friends / family, making a drink, using an everyday object, lifting, moving or carrying everyday objects such as chairs, bags etc.)
- Attended school or preschool (if school age and term time)? Y/N
- Able to do full activities (Full activity is all the normal activities above plus full activity – e.g. sport, dance, playing with friends or other activity that your child normally takes part in.) Y/N
- Parents' missed work due to child's appendicitis? Y/N

The following data will be collected weekly at 1, 2, 3 and 4 weeks via a smartphone app

- The CHU 9D (proxy and self-report where appropriate)
- The last week have you had any contact with a health care professional(s) for your child's appendicitis? Y/N

Site staff will check the database regularly and contact any patients who have not provided data as a prompt to complete.

Follow-up appointments will take place at 6 weeks, 4 months, 8 months and 12 months following randomisation in the outpatient clinic or Clinical Research Facility at each participating centre. The 4, 8- and 12-month appointments should be completed over the phone. The follow up appointments should be completed no earlier than 1 week before the projected visit date, and no later than 2 weeks after the projected visit date.

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.

Parents/Carers should be contacted up to 3 times by telephone, letter or email, as appropriate, before 'missed visit' can be recorded in the database. If a visit is missed, the patient and parent/carer will still remain in the study for follow up at later timepoints. If the missed visit takes place at the final 12 month visit, data collection regarding routine data will be requested.

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

- CSRI
- CHU 9D proxy and self-reported (where appropriate)
- 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

- Wound infection
- Antibiotic failure
- Outcome of physical exam (if completed as part of standard care)

Patients completing all follow up appointments and questionnaires will be given a gift voucher (via email) as a thank you for taking part in the study.

We will also seek consent from parents to determine if they are happy to be contacted 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 follow up only. This activity is outside of the current funding remit and will obtain ethical approval prior to being completed.

# 15 DEVIATIONS AND SERIOUS BREACHES

Any Trial 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.

All serious protocol deviations/violations and serious breaches of Good Clinical Practice and/or the Trial protocol will immediately be reported to the regulatory authorities and other organisations, as required in the Medicines for Human Use (Clinical Trials) Regulations 2004, as amended.

# 16 TRIAL DISCONTINUATION

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

## *16.1 Reasons for Trial discontinuation*

Participants may be discontinued from the Trial 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 Trial discontinuation should be recorded in the eCRF and medical record.

# 17 WITHDRAWAL

The participant / legal representative is free to withdraw consent from the trial 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.

Withdrawal criteria will be explained to the patients/parents. 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 Doctor/Surgeon. 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 trial withdrawal (date, reason if known) should be recorded in the eCRF and medical record. The withdrawal options are as follows.

- Completed – this includes patients who have not attended the 12 month follow up visit but information regarding complications, histology (if available) and readmission is available
- Death
- Withdrawal by subject and request that no further data is collected from hospital notes
- Other – lost-to-follow-up or site terminated by Sponsor.

# 18 PROHIBITED AND RESTRICTED THERAPIES DURING THE TRIAL

None

# 19 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.

# 20 SAFETY

## 20.1 DEFINITIONS

**Adverse Event (AE):** any untoward medical occurrence in a participant or clinical Trial participant which does not necessarily have a causal relationship with Trial 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 Trial treatment or participation (regardless of causality assessments).

**Serious Adverse Event (SAE)**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**.

*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.

## 20.2 SERIOUSNESS

An assessment of the seriousness must be undertaken by a medically qualified doctor who is appropriately listed on the trial delegation log; this is usually the investigator.

All reportable SAEs must be reported immediately by the participating centre to the SCTU. Please see the following sections to determine what is reportable.

## 20.3 CAUSALITY

An 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 Doctors/Surgeons may be asked for advice in these cases.

In the case of discrepant views on causality, SCTU will classify the event as per the worst-case classification and if onward reporting is required, the applicable Research Ethics Committee will be informed of both parties' points of view.

| Relationship | Denoted |
|---|---|
| Related - There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out. | Related and expected SAE/ Related and unexpected SAE |
| Unrelated - There is no evidence of any causal relationship | SAE |

## 20.4 NON-SERIOUS ADVERSE EVENTS

Of AEs deemed to be non-serious, only those considered related to the trial interventions (rather than solely related to the appendicitis itself) need to be recorded on the relevant eCRF. However the following adverse events *do not* require recording on the adverse event eCRF if they are not serious:

- Fever
- Vomiting
- Diarrhoea
- Non-recurrent abdominal pain

## 20.5 SERIOUS ADVERSE EVENTS

For this trial, only SAEs deemed related to the trial intervention (see definition in section 20.3 above) and not in the list of exceptions below need to be reported to the SCTU as SAEs

### *20.5.1 Exceptions for SAE Reporting*

For the purposes of this trial, the following SAEs do not require reporting to SCTU using the Serious Adverse Event Report Form:

A. Hospitalisations:
   - 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
   - Hospitalisations for an unrelated condition

B. Related to operative management:
   - Intra-operative damage to surrounding anatomical structures including but not limited to bowel loops, urethra, vessels, Fallopian tubes, ovaries
   - Post-operative hypertrophic scar (cheloid)
   - Recurrent abdominal pain

C. Related to non-operative management:
   - Adverse events related to antibiotic use as per product monographs
   - Recurrent abdominal pain
   - Intra-abdominal or pelvic abscess formation.

D. Related to either treatment arm:
   - Fever
   - Vomiting
   - Diarrhoea
   - Non-recurrent abdominal pain

If any of these excluded events occur ***and*** they meet the seriousness criteria ***and*** they are deemed related to the trial intervention, then these should be reported as Adverse Events on the eCRF.

## 20.6 EXPECTEDNESS

Expectedness assessments for SAEs are made, by SCTU on behalf of the Sponsor, against the list of expected events below.

A. 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) Post-operative hypertrophic scar (cheloid)
   (iii) Recurrent abdominal pain
B. Related to non-operative management:
   (i) Adverse events related to antibiotic use as per product monographs
   (ii) Recurrent abdominal pain
   (iii) Intra-abdominal or pelvic abscess formation.
C. Related to either treatment arm:
   (i) Fever
   (ii) Vomiting
   (iii) Diarrhoea
   (iv) Non-recurrent abdominal pain

The nature or severity of the event 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'.

## 20.7 REPORTING

### *20.7.1 Timelines*

All reportable SAEs and AEs should be reported from informed consent to 12 months after randomisation.

All unresolved SAEs and / or AEs should be followed by the investigator until resolved or an end of trial criteria is met (i.e. lost to follow up, withdrawal etc).

### *20.7.2 Reporting Details*

For all reportable **SAEs** an SAE report form should be completed with as much detail as possible (including any relevant anonymised treatment forms and/or investigation reports) and emailed to SCTU immediately but at least within 24 hours of site becoming aware of the event.

**Or**

Contact SCTU by phone to report the event and then email a scanned copy of the SAE report form completed as above as soon as possible.

**SAE REPORTING CONTACT DETAILS**

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

**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 report is not complete at the time of reporting.

The event term should be the most appropriate medical term/concept. Grades should be given in accordance with the NCI CTCAE v5.

20.7.3 ***Pre-existing Conditions***

Pre-existing conditions (prior to informed consent) as specified on the Medical History eCRF should not be reported as an AE unless the conditions worsens during the trial and it is deemed related to the trial intervention.

## 20.8 RESPONSIBILITIES

### *20.8.1 Principal Investigator (PI):*

The PI, or medically qualified doctor who is registered on the delegation of responsibility log, is responsible for:

a) Using medical judgement in assigning seriousness, causality and if requested, whether the event was anticipated using the expectedness information approved for the trial (as detailed in Section 6.4)
b) Ensuring that all reportable SAEs are recorded and reported to the SCTU immediately, or at a least within 24 hours, of becoming aware of the event and provide further follow-up information as soon as available. Ensuring that SAEs are chased with the SCTU if a record of receipt is not received within 1 working day of initial reporting.
c) Ensuring that AEs are recorded and reported to the SCTU in line with the requirements of the protocol.

### *20.8.2 Chief Investigator (CI)/delegate or independent clinical reviewer:*

The CI, or delegated clinical reviewer, is responsible for:

a) Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk / benefit.
b) Using medical judgement in assigning the SAEs seriousness, causality and whether if requested, the event was anticipated (in line with the expectedness information) where it is required as a second clinical opinion or if it has not been possible to obtain local medical assessment.
c) Using medical judgement in assigning whether the event was anticipated using the expectedness information approved for the trial (as detailed in Section 6.4).
d) Immediate review of all Related and Unexpected SAEs.

e) Review of specific SAEs and related SAEs in accordance with the trial risk assessment and protocol as detailed in the Trial Monitoring Plan.
f) Upon request review coding decisions

#### *20.8.3 Sponsor/delegate:*

The Sponsor, or delegate, is responsible for:

a) Central data collection and verification of AEs and SAEs, according to the trial protocol onto a database/paper forms.
b) Reporting safety information to the CI, delegate or independent clinical reviewer for the ongoing assessment of the risk / benefit according to the Trial Monitoring Plan.
c) Checking causally related events against the approved expectedness information, in place at time of event onset.
d) Reporting safety information to the independent oversight committees identified for the trial (Data Monitoring & Ethics Committee (DMEC) and / or Trial Steering Committee (TSC)) according to the Trial Monitoring Plan.
e) Ensuring that expedited reporting of related and unexpected serious adverse events to the REC are within the required timelines.
f) Notifying Investigators of related and unexpected serious adverse events that occur within the trial.

### 20.9 REPORTING URGENT SAFETY MEASURES

If any urgent safety measures are taken the CI/Sponsor shall immediately, and in any event no later than 3 days from the date the measures are taken, give written notice to the REC of the measures taken and the circumstances giving rise to those measures.

## 21 STATISTICS AND DATA ANALYSES

### 21.1 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 between 9am and 5pm. Minimisation will be used to ensure similarity between the groups in factors that may affect diagnostic accuracy and outcome of treatment using the following criteria:

(i) Age: [4-8yrs]; [9-15yrs]
(ii) Sex: [Male]; [Female]
(iii) At the time of diagnosis how long have they had abdominal pain for? (<48 or ≥48 hours)
(iv) Centre

### 21.2 SAMPLE SIZE

Rates of treatment success in each treatment arm are predicted as follows:

- Appendicectomy arm: post-operative complication requiring intervention under general anaesthesia 2%, negative appendicectomy 10% (total 12%) - anticipated treatment success = 88%.
- Non-operative treatment arm: failure of antibiotic treatment 5%, recurrence 15% (total 20%) so anticipated treatment success = 80%.

We therefore anticipate a difference between the treatment arms with respect to the primary outcome of 8 percentage points. Since there are potential further benefits to non-operative treatment that are not included within the primary outcome (e.g. greater parental acceptability, avoidance of surgical complications, cost) it is appropriate to use a wider non-inferiority margin for our analysis. The size of this non-inferiority margin was explored with both surgeons and parents in our feasibility study. Whilst it was evident that parents would accept a wider non-inferiority margin since they are particularly attracted to the potential benefits of non-operative treatment, surgeons are not willing to accept a margin of greater than 20%. We have therefore pre-specified a 20% non-inferiority margin for this trial. Of interest this is the same margin that was defined by a Cochrane review as being 'clinically relevant'[30]. Based on these estimates, with a one-sided 5% significance level and 90% power, this trial will require a total of 318 cases analysed at 1 year (159 per arm), which gives a recruitment target of 376 participants (188 per arm) to allow for a 15% loss to follow up rate.

### 21.3 INTERIM ANALYSIS

Internal pilot data will be analysed after 12 months from the start of recruitment to assess trial and recruitment progress and is described in a later section.
All data from the internal pilot and subsequent RCT will be used in the final analysis. No interim analysis of effectiveness is planned. Data will be presented according to the CONSORT guidelines extension for non-inferiority trials, 2012[31].

### 21.4 STATISTICAL ANALYSIS PLAN (SAP)

The study will be reported in accordance with CONSORT guidelines. A detailed statistical analysis plan will be written and reviewed prior to the trial database being frozen. All data and appropriate documentation will be stored for a minimum of 10 years after the completion of the trial. All assumptions underlying regression modelling applied will be checked and alternative analysis methods used (e.g. transformation or non-parametric methods) if the assumptions are not met.

Characteristics at trial entry will be summarised separately by randomised group using counts and percentages for categorical variables, means and standard deviations for normally distributed continuous variables, or medians and interquartile ranges for non-normally distributed continuous variables.

The primary analysis will compare the overall 'non-operative pathway' versus appendicectomy and will take into account whether the initial non-operative approach was successful or not by designating per-protocol treatment switches to appendicectomy as treatment failure. This analysis, based on a comparison of two treatment *pathways* rather than non-operative treatment versus appendicectomy, reflects the proposed clinical pathway under investigation. It also accounts for treatment switches due to non-operative treatment failure by designating these as a treatment failure at 1 year (the primary outcome). If the non-operative treatment pathway is inferior to appendicectomy, this will be reflected in the numbers of patients who switch to appendicectomy and this will be reflected in the analysis proposed.

It is noted that from a standard statistical perspective, this is neither a true per-protocol, nor a true Intention To Treat (ITT) analysis but a hybrid of the two which designates the outcome as a treatment failure if the treatment is switched to appendectomy when the non-operative treatment has failed, yet considers such patients as 'per-protocol' according to the overall treatment pathway and keeps them in the non-operative treatment arm for analysis (for both standard ITT and per-protocol analyses).

Additionally, it is noted that consideration has been given to alternative analyses that would be useful and meaningful to Doctors, Surgeons and Healthcare Professionals and recognise that some kind of

direct comparison between the two treatment arms rather than between the two treatment pathways might be desirable. Three alternative analyses were considered:

- An ITT analysis comparing non-operative treatment with appendicectomy. However, this is likely to overestimate the efficacy of the non-operative treatment, since it would not account for treatment successes that have occurred due to treatment switches to appendicectomy (as they would be counted as treatment successes in the non-operative treatment group). Such an analysis would give no information at all on the actual efficacy or otherwise of the non-operative treatment.
- A per-protocol analysis comparing non-operative treatment with appendicectomy. However, this is also likely to overestimate the efficacy of the non-operative treatment, since the only patients that would be analysed in that treatment arm would be those who, by definition, have successfully completed non-operative treatment and remain well and thus have not required an appendicectomy, thus ensuring a 100% success rate in the non-operative treatment arm.
- A complier average causal effect (CACE) analysis, in order to account for treatment switches to appendicectomy. However, treatment switches in this study, based on our findings in our feasibility study, will be mainly driven by failure of the non-operative treatment and not by non-compliance. So although a CACE analysis generally aims to identify the causal effect of actually receiving a specified treatment, it would not achieve this in our study.

It is recognised that in order to reflect acceptable clinical practice in this pragmatic trial, the primary analysis has drawbacks and may be complex to interpret. This context, and especially the issue of switched treatment to appendectomy, will be explored fully in the presentation of results and any conclusions we draw from the study findings.

Analysis of the primary outcome (treatment success at 1 year) will be by a mixed effects logistic regression model controlling for the minimisation factors with age, sex and onset of pain duration as fixed effects, each with two levels and study site (10 or more levels) as a random effect. It is possible that controlling for study site will not be possible due to stability of the statistical model and this will be explored. Analysis will produce the absolute risk difference between the two treatment arms with a one-sided 95% confidence interval which can then be assessed against the pre-specified non-inferiority margin of 20% (see sample size section for justification of this). The number and percentage of children meeting the definition of treatment success at 1 year following randomisation will also be presented.

As described above, therefore, the primary outcome analysis will be on an ITT basis and patients will be analysed in the treatment group to which they were assigned regardless of deviation from the protocol or treatment received. Of note children randomised to the non-operative pathway who commence non-operative treatment but are later switched to appendicectomy due to clinical deterioration or lack of clinical improvement will be classed as experiencing a ‘treatment failure’ but will still remain on the per-protocol non-operative pathway. The same is true of children randomised to the non-operative pathway who initially respond to this treatment, are discharged and who are then readmitted with a recurrence of appendicitis which will then be treated with an operation. Thus, such children would be analysed in the non-operative pathway in either an ITT or a per-protocol analysis. The only children who would be treated differently in the ITT analysis to a per-protocol analysis in this trial are those who withdraw from their allocated treatment and those who have appendicectomy when the non-operative treatment pathway has not been followed.

A per-protocol analysis may therefore be useful to explore the effect of protocol deviations, which in CONTRACT were uncommon (4 of 57, 7%). In this trial protocol deviations are most likely to be due to parents’, children’s, Doctors, Surgeons or Healthcare Professionals desire to revert to appendicectomy treatment ahead of the trial schedule rather than due to an assessment of clinical inferiority of the non-operative arm. Thus the per-protocol analysis will be a secondary analysis.

Sub-group analysis exploring outcomes from laparoscopic versus open procedures was considered but given the likely lack of open procedures (2 of 35 procedures in CONTRACT) may not be possible or meaningful. Secondary outcomes will be analysed according to an agreed statistical analysis plan. Individual outcomes that contribute to the composite primary outcome will be presented solely as descriptive statistics within the treatment pathway to which they apply. Secondary outcomes that apply to both treatment pathways will be analysed in superiority comparisons between the treatment pathways in ITT analyses. Additionally, secondary outcomes will be reported separately for children in the non-operative treatment arm in whom non-operative treatment is not successful and who subsequently undergo appendicectomy.

Sub-group analyses exploring study recruitment and outcomes in specialist paediatric centre versus DGH recruiting sites will be conducted.

All analyses will be carried out using STATA and/or SAS.

# 22 REGULATORY

## 22.1 CLINICAL TRIAL AUTHORISATION

This trial 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.

## 22.2 ETHICAL CONSIDERATIONS

The trial 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 UK Regulations. Each participant's consent to participate in the trial 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 trial without giving reasons must be respected.

After the participant has entered the study, the Doctor or Surgeon 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 trial 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 trial follow-up without giving reasons and without prejudicing their further treatment.

## 22.3 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[32-35] and participants will be counselled accordingly. The safety of participants will be further enhanced by the formation of the DMEC as outlined below.

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 all families to hold their personal details in a secured registry and to contact them in the future as part of a future ethically approved project to discuss their childs health and determine if those in the non-operate treatment group 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 or guaridians 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 wherever possible consent will be obtained within 4 hours of first discussion of the study. Where specific circumstance mean that it is both appropriate and acceptable to delay making a decision the absolute maximum time between first discussing the study and obtaining consent will be 18 hours. The research process will never impede on provision of safe and effective patient care.

## 22.4 ETHICAL APPROVAL

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

An annual progress report will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended.

Within one year after the end of trial, the Chief Investigator will submit a final report with the results, including any publication/abstracts, to the REC.

## 22.5 INFORMED CONSENT PROCESS

Informed consent is a process that is initiated prior to an individual agreeing to participate in a trial 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 trial 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 trial 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.

### 22.6 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 e/CRFs participants will not be identified by their names, but by an identification code.

Any data collected as part of the trial will be securely stored in line with the Data Protection Act and GDPR.

## 23 SPONSOR

This Trial is sponsored by University Hospital Southampton NHS Foundation Trust.

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

### 23.1 INDEMNITY

For NHS sponsored research HSG (96) 48 reference no.2 applies. If there is negligent harm during the clinical trial 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.

### 23.2 FUNDING

NIHR Health Technology Assessment Programme are funding this study.

#### *23.2.1 Site payments*

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

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

#### *23.2.2 Participant payments*

Participants will be offered a £15 gift voucher on completion of all follow up timepoints up to 12 months post randomisation.

### 23.3 AUDITS AND INSPECTIONS

The trial may be participant to inspection and audit by University Hospital Southampton NHS Foundation Trust (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.

# 24 TRIAL OVERSIGHT GROUPS

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

## 24.1 TRIAL MANAGEMENT GROUP (TMG)

The TMG is responsible for overseeing progress of the study, including both the clinical and practical aspects. The Chair of the TMG will be the Chief Investigator of the study.

The CONTRACT 2 TMG charter defines the membership, terms of reference, roles, responsibilities, authority, decision-making and relationships of the TMG, including the timing of meetings, frequency and format of meetings and relationships with other trial committees.

## 24.2 TRIAL STEERING COMMITTEE (TSC)

The TSC act as the oversight body on behalf of the Sponsor and Funder. The TSC will meet at least twice a year via teleconference or in person where possible. The majority of members of the TSC, including the Chair, should be independent of the trial.

The CONTRACT 2 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.

## 24.3 INDEPENDENT DATA MONITORING COMMITTEE (IDMC) /DATA MONITORING AND ETHICS COMMITTEE (DMEC)

*(**NB** for the purposes of this protocol, IDMC and DMEC refer to the same committee, and these terms can be used interchangeably).*

The aim of the IDMC is to safeguard the interests of trial participants, monitor the main outcome measures including safety and efficacy, and monitor the overall conduct of the study.

The CONTRACT 2 DMEC charter defines the membership, terms of reference, roles, responsibilities, authority, decision-making and relationships of the IDMC, including the timing of meetings, methods of providing information to and from the IDMC, frequency and format of meetings, statistical issues and relationships with other trial committees.

# 25 DATA MANAGEMENT

Participant data will be entered remotely at site and retained in accordance with the current Data Protection Regulations. 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 trial 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 Participant Information Sheet and Informed Consent Form will outline 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 trial 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 trial 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 trial 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 data and audit trail returned to the PI for each participant.

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

## 26 DATA SHARING REQUESTS FOR RESULTS THAT ARE AVAILABLE IN THE PUBLIC DOMAIN

In order to meet our ethical obligation to responsibly share data generated by interventional clinical trials, SCTU operate a transparent data sharing request process. As a minimum, anonymous data will be available for request from three months after publication of an article, to researchers who provide a completed Data Sharing request form that describes a methodologically sound proposal, for the purpose of the approved proposal and if appropriate a signed Data Sharing Agreement. Data will be shared once all parties have signed relevant data sharing documentation.

Researchers interested in our data are asked to complete the Request for Data Sharing form (CTU/FORM/5219) [template located on the SCTU web site, www.southampton.ac.uk/ctu] to provide a brief research proposal on how they wish to use the data. It will include; the objectives, what data are requested, timelines for use, intellectual property and publication rights, data release definition in the contract and participant informed consent etc. If considered necessary, a Data Sharing Agreement from Sponsor may be required.

# 27 MONITORING

### 27.1 CENTRAL MONITORING

Data stored at SCTU will be checked for missing or unusual values (including range checks) and checked for consistency within participants over time. Data queries on eCRFs will be raised to site either automatically or manually by STCU staff via the database. Sites should respond to queries on the database and provide an explanation/resolution to any discrepancies within the required timeframe. Queries and responses are recorded within the database audit trail. There are a number of monitoring

principles in place at SCTU to ensure reliability and validity of the trial data, which are detailed in the trial monitoring plan."
The DMEC also have responsibility for specific central monitoring activities, as described in protocol section 24.3

### 27.2 CLINICAL SITE MONITORING

Monitoring will be completed as per the trial monitoring plan

#### *27.2.1 Source Data Verification*

On receipt of a written request from SCTU for a triggered monitoring visit, 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 trial 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 trial site without informed consent

### 27.3 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.

The PI is responsible for maintaining the Investigator Source Location Agreement (CTU/FORM/5245) to detail site specific source data location information.

## 28 RECORD RETENTION AND ARCHIVING

Trial 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 trial to be fully documented and the trial data to be subsequently verified. After trial closure the PI will maintain all source documents and trial related documents. All source documents will be retained for a period of 10 years following the end of the trial.

Audio recordings and transcripts collected as part of the communication study will be stored at the University of Liverpool for up to 10 years after the end of the study (or deleted at the end of the study if the participants decline to consent to this) following the local data protection policy and guidelines.

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

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

## 29 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 Trial Management Group (TMG} has published its report. The TMG 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.

### 29.1 DISSEMINATION

If they consent to receiving the information, patients or parents will be notified of the results of the trial via the site where they were recruited. The data will be published in a peer reviewed journal and available in the public domain. Our Study Specific Advisory Group (SSAG) will write the report to ensure the language is appropriate and accessible.

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# 31 APPENDICES

**Appendix 1 - *Health Economic secondary care data collection***

The Participating Sites (hospitals, trusts) that have incorporated PLICs methodology on their systems, would be expected to provide PLICs data for each study participant. PLICs data refers to each index hospital admission and also any related subsequent admissions (e.g. for related complications should they occur). The data for each patient will include 2 tables from the summary section of the PLICs collection template:
(1) Costs by Fixed/Variable and
(2) Costs by Cost Pool Groups.

Providers that have not yet implemented PLICs will be expected to provide HRG codes used for patients participating in the study. This will be following the method that was in place before the introduction of PLICs, collecting reference costs in order to allow identifying activity and costs. This method also refers to each index hospital admission and also any related subsequent admissions (e.g. for related complications should they occur). This method of data collection will include a table with the *Admitted patient care and outpatient procedure (APC & OPROC) HRG codes* as were applied for each patient. For example, for the appendicectomy procedure this could be the HRG code: FF37G.

In both cases the individual patient data will be anonymised using the study ID number prior to delivery for analysis. The study health economist won't have access to personal information or other identifiers.

Each participating centre would be expected to provide the name and contact details of one individual that could be contacted by the lead health economist of the CONTRACT 2 study (M.Chorozoglou@soton.ac.uk) during the life of the study making arrangements and securing the timely collection and delivery of the relevant data. This for example could be to discuss potential alternative solutions when the costing systems are not linked in fully to the PLICS.

Data collection template for providers using PLICs:

| **Table 1** | |
|---|---|
| **Costs by Fixed/Variable** | |
| **Cost Type** | **Value (£)** |
| Fixed Costs | £0.00 |
| Semi Fixed Costs | £0.00 |
| Variable Costs | £0.00 |
| **Total** | **£0.00** |

| **Table 2** | |
|---|---|
| **Costs by Cost Pool Groups** | |
| **Cost Type** | **Value (£)** |
| Blood and Blood Products | £0.00 |
| CNST | £0.00 |
| Critical Care | £0.00 |
| High Cost Drugs | £0.00 |
| Chemotherapy Drugs | £0.00 |
| All Other Drugs | £0.00 |
| Emergency Department | £0.00 |
| Imaging - Medical Staffing | £0.00 |

| | |
|---|---|
| Imaging - All Other Costs | £0.00 |
| Medical Staffing (excluding Imaging, Pathology & Other Diagnostics) | £0.00 |
| Operating Theatres | £0.00 |
| Other Clinical Supplies and Services | £0.00 |
| Other Diagnostics Tests - Medical Staffing | £0.00 |
| Other Diagnostics Tests- All Other Costs | £0.00 |
| Outpatients | £0.00 |
| Pathology- Medical Staffing | £0.00 |
| Pathology- All Other Costs | £0.00 |
| Pharmacy Services | £0.00 |
| Prostheses/Implants/Devices | £0.00 |
| Radiotherapy | £0.00 |
| Secondary Commissioning Costs | £0.00 |
| Specialist Procedure Suites excluding Endoscopy Units | £0.00 |
| Specialist Procedure Suite - Endoscopy Units Only | £0.00 |
| Specialist Nursing Staff | £0.00 |
| Therapies | £0.00 |
| Wards | £0.00 |
| Overheads | £0.00 |
| Impairments | £0.00 |
| **Total of cost elements** | **£0.00** |

## SUMMARY OF SIGNIFICANT CHANGES TO THE PROTOCOL

| Protocol date and version | Summary of significant changes |
|---|---|
| V1 26th Aug 2021 | First written |
| V2 29th Sep 2021 | Minor clarification of randomisation stratification factors<br>Appendix 1 added detailing health economic data collection |
| V3 10th Nov 2021 | Maximum time between first discussing the study and obtaining consent increased to 18 hours to allow for evening or overnight admissions.<br>Rewording of exclusion point 9 to allow second line antibiotics |
| V4 26th July 2022 | Screening details updated to reflect information captured<br>Pilot phase progression criteria corrected to reflect funding submission<br>Pregnancy notification removed in section 20.10<br>Week 4 visit window corrected in schedule of events<br>Section 21.4 - Statistical analysis plan updated |
| V5 18th January 2023 | Added and removed certain information on the schedule of events and secondary endpoints<br>Updated information and clarification on consent and screening procedures<br>Updated information and clarification on the Communication Sub-study processes<br>Updated information and clarification on the future research data collection/study<br>Other small typographic changes and re-wording |
| V6 5th April 2023 | Change to temperature and units for CRP, typographical error<br>Other small typographical changes |
| Version 7 05 Jun 2024 | Update to protocol regarding Communication Sub-Study closing, update regarding training during recruitment phase, update regarding the transfer of Informed Consent Forms, update to screening procedure of collecting additional information regarding Complicated Appendicitis Score, clarification of criteria for patients being discharged home, update to the safety section, additional information provided regarding sub-group analysis and clarification in data section on use of wording and other sections |
| Version 8 30-Oct-2024 | Update to protocol regarding the communication sub-study closing to recruitment, update regarding the Gillick competency and re-consenting where this is required by site, update to the completion of the complicated appendicitis score where the completion of one or more points is not clinically indicated, update regarding training during the recruitment phase for new and existing sites, update regarding the process for transferring informed consent forms as NHS.net no longer exists, clarification added for patients being discharged home, update to the safety section, additional information provided regarding sub-group analysis and clarification in data section on use of wording, clarification to the complicated appendicitis score regarding what is classed as rebound tenderness, clarification of other wording throughout protocol |