CONTRACT Study - CONservative TReatment of Appendicitis in Children (feasibility): study protocol for a randomised controlled Trial

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Abstract

Currently, the routine treatment for acute appendicitis in the UK is an appendicectomy. However, there is increasing scientific interest and research into non-operative treatment of appendicitis in adults and children. While a number of studies have investigated non-operative treatment of appendicitis in adults, this research cannot be applied to the paediatric population. Ultimately we aim to perform a UK based multicentre randomised controlled trial (RCT), to test clinical and cost effectiveness of non-operative treatment of acute uncomplicated appendicitis in children compared to appendicectomy. First, we will undertake a feasibility study to assess the feasibility of performing such a trial.

Methods:

The study involves a feasibility RCT with nested qualitative research to optimise recruitment and a health economic sub-study. Children (aged 4-15 inclusive) diagnosed with acute uncomplicated appendicitis that would normally be treated with an appendicectomy are eligible for the RCT.

Exclusion criteria include clinical/radiological suspicion of perforated appendicitis, appendix mass or previous non-operative treatment of appendicitis. Participants will be randomised into one of two arms. The intervention arm is treated with antibiotics and regularly clinical assessment to ensure clinical improvement. The control arm will receive appendicectomy. Randomisation will be minimised by age, gender, duration of symptoms and centre. Children and families who are approached for the RCT will be invited to participate in the embedded qualitative sub-study which includes recording of recruitment consultants and subsequent interviews with participants and non-participants and their families, and recruiters. Analyses of these will inform interventions to optimise recruitment. Main study outcomes include recruitment rate (primary outcome), identification of strategies to optimise recruitment, performance of trial treatment pathways, clinical outcomes and safety of non-operative treatment. We have involved children, young people and parents in study design and delivery.

Discussion:

This study will explore the feasibility of performing a full, efficacy RCT comparing non-operative treatment with appendicectomy in children with acute uncomplicated appendicitis. Factors determining success of the current study include recruitment rate, safety of non-operative treatment, and adequate interest in the future RCT. Ultimately this feasibility study will form the foundation of the main RCT and reinforce its design.

Registration:

ISRCTN, ISRCTN15830435. Registered 8 February 2017, http://www.isrctn.com/ISRCTN15830435

Keywords:

Appendicitis, non-operative treatment, paediatric surgery, appendicectomy, feasibility

Background

Acute appendicitis is the most common surgical emergency in children [1]. The lifetime risk of developing appendicitis is 7-8% and the most common age for developing appendicitis is in the early teens. Appendicectomy is considered the gold standard treatment for acute appendicitis by most

surgeons but many parents and patients find the prospect that their child needs emergency surgery frightening and one they are keen to avoid if an alternative is available [2]. Preliminary work we have already undertaken with children and families confirms a high level of interest in non-operative treatment and indeed a preference for non-operative treatment so long as clinical outcomes are comparable.

Although appendicectomy is considered a simple procedure, it requires a general anaesthetic and an abdominal operation with its associated risks. The complication rate of appendicectomy (including wound infection, intra-abdominal abscess, and adhesional small bowel obstruction) is up to 25% [3] with a need for hospital readmission in 4-5% of cases [4, 5]. A contemporary estimation of these risks is available from the National Appendicectomy Audit, a nationwide audit of outcomes of appendicectomy for acute appendicitis in 19 Specialist Paediatric Surgery Centres in the UK [6]. Over a 2 month period, 242 appendicectomies for acute appendicitis were performed. The negative (histologically normal) appendicectomy rate was 10.3% and the 30-day adverse event (AE) rate (a composite of readmission, re-intervention, pelvic collection and wound infection) was 15.3%.

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

An alternative approach to treating acute appendicitis in children would be treatment with antibiotics and without an appendicectomy. Whilst there is growing scientific interest in the use of non-operative treatment with antibiotics due to its potential benefits over surgery and existing data to support its safety, the relative efficacy of this approach compared to appendicectomy is not yet known [7] . Using a non-operative approach to treat appendicitis, patients may avoid the mental and physical stress and trauma of an operation as well as the associated complications. Non-operative treatment has the potential to reduce the quantity of resources used by the National Health Service (NHS). For example,

by reducing the amount of theatre time, staff time and surgical resources used for the treatment of appendicitis, there could be significant savings for the NHS.

It has been known for some time that acute appendicitis can be treated successfully by antibiotics alone, in the context of remote environments without surgical service capability [8]. However, the role of non-operative treatment as primary therapy has only recently come under consideration in developed healthcare systems, initially in adults [3, 9-15], and more recently in children [16-18]. Although studies in adults are sometimes extrapolated to children, to do so is problematic since there are key differences in appendicitis occurring in adults compared to children. The presentation of appendicitis and the intra-abdominal inflammatory response is different in adults and children [19, 20] and may be more amenable to antibiotic treatment alone, and the psychosocial and economic impact of appendicitis in children affects the whole family, rather than just the individual. Therefore, a paediatric RCT is necessary to compare both treatment options.

There is just one pilot RCT, recently performed in Sweden, comparing non-operative treatment with antibiotics with appendicectomy in children with acute appendicitis [18]. Fifty children (aged 5-15 years) with acute non-perforated appendicitis were randomised to antibiotics (n=24) or appendicectomy (n=26). All children in the surgery group had histopathologically-confirmed acute appendicitis and none experienced a significant surgical complication. In the antibiotic group, 2 of 24 underwent appendicectomy within the time of primary antibiotic treatment, and 1 further child required appendicectomy for histologically-proven, recurrent acute appendicitis 9 months later. Of eligible participants, the recruitment rate was 40%, the drop-out rate following treatment allocation was 2% (1 patient) and no patient was lost to follow-up by 1 year. This pilot study was not powered sufficiently to compare the efficacy of antibiotics versus surgery, but was conducted to inform the design of an international, multicentre RCT which is currently recruiting in non-UK centres [21].

Our group have recently performed a systematic review and meta-analysis comparing the efficacy of non-operative treatment and appendicectomy for uncomplicated appendicitis in children [7]. Whilst

there were limitations related to a lack of RCTs, the existing data support a position of equipoise between these two treatment approaches. Neither this review nor any of the contributing studies [16-18, 22-24] identified any safety concerns regarding non-operative treatment.

In addition to outcomes of the acute illness, the development of recurrent appendicitis is an important consideration in children who receive non-operative treatment that is not applicable to children treated with appendicectomy. In adults [9-12, 25] the incidence of recurrence (within 1 year) is around 15%. A recent pilot study of non-operative treatment of appendicitis in children with 1 year follow-up reported a recurrence rate of 5% [18] and our recent systematic review estimated an incidence of 14% [7]. This is the best current estimate in children.

Given the current uncertainty, regarding the relative efficacy and cost-effectiveness of non-operative treatment compared to appendicectomy in children with uncomplicated acute appendicitis, a definitive RCT is necessary. Although RCTs are ongoing in other countries [26, 27] there are important differences in diagnostic techniques and healthcare delivery in the UK that mandate a UK specific trial. These include a much lower reliance on diagnostic imaging for confirmation of appendicitis in the UK compared to other countries, a higher negative appendicectomy rate and a lower uptake of laparoscopic appendicectomy in the UK, all of which may influence relative efficacy of non-operative treatment compared to surgery [6, 28]. Prior to performing a large efficacy trial, we designed this feasibility study, which includes a feasibility RCT, to inform the design and conduct of a future RCT and establish whether a main trial is possible in the UK.

Methods/Design

Study Design:

The CONTRACT study comprises:

1. A randomised controlled feasibility trial of children comparing a non-operative treatment pathway with appendicectomy. A standardised treatment pathway (Figure 1) will be used in each arm of the study beginning with broad-spectrum antibiotics from the point of enrolment. One arm will

then undergo urgent appendicectomy while the other will be treated non-operatively with continuation of broad-spectrum antibiotics. Both treatment pathways will receive the same follow up schedule.

2. A detailed programme of embedded qualitative and quantitative research to optimise recruitment to the feasibility RCT. It will also inform the design and conduct of any future RCT of non-operative treatment versus appendicectomy in the treatment of acute uncomplicated appendicitis in children.
3. A health economics (HE) feasibility study to allow the identification of key cost drivers and other parameters necessary to perform a full economic evaluation in our future RCT. This will include the design and piloting of data collection tools and adoption of a micro-costing approach. A full protocol of the HE sub-study is described separately.
4. The development of a Core Outcome Set (COS) for the non-operative treatment of children with uncomplicated acute appendicitis for use in the future RCT as well as the wider research community. A full protocol for the COS is published elsewhere [29].
5. A patient and public involvement (PPI) work stream that reciprocally feeds into elements 1, 2 and 4 (above). We have formed a Study Specific Advisory Group (SSAG) made up of children who have had acute uncomplicated appendicitis, children who have not, and parents.

1. Randomised Controlled Feasibility Trial

Population:

Children aged 4-15 inclusive, with a clinical diagnosis of acute appendicitis who would normally be treated with an appendicectomy as part of their standard care. Patients will be identified by the clinical team at the time of diagnosis and their eligibility will be confirmed by the research team as soon as possible.

Inclusion criteria:

- Children age 4 – 15 years (>3 and <16 years)

- Clinical diagnosis, either with or without radiological assessment, of acute appendicitis which prior to study commencement would be treated with appendicectomy
- Written informed parental consent, with child assent if appropriate

Exclusion criteria:

- Clinical signs or radiological findings to suggest perforated appendicitis
- Presentation with appendix mass
- Previous episode of appendicitis or appendix mass treated non-operatively
- Major anaesthetic risk precluding allocation to the appendicectomy arm
- Known antibiotic allergy preventing allocation to non-operative treatment arm
- Antibiotic treatment started at referring institution (defined as 2 or more doses administered)
- Cystic fibrosis
- Positive pregnancy test
- Current treatment for malignancy

Randomisation:

Eligible patients will be identified, approached and consented by the treating clinician. After written informed consent, a member of the trial team at site will randomised the participant to one of two treatment groups in a 1:1 ratio via an independent web-based system (TENALEA). This online system allows complete pre-randomisation concealment of treatment allocation and provides instant assignment to either the Appendicectomy or Non-Operative treatment group. Minimisation will be used to account for recruiting centre and ensure balance between the groups in factors that may affect diagnostic accuracy and outcome of treatment. The factors which are taken into account are a) Gender: Male; Female, b) Age: 4-8; 9-15, c) Duration of symptoms (onset of pain to recruitment into study): <48 hours; ≥48 hours, and d) Recruiting centre.

Interventions

Figure 1: Clinical pathway for both treatment arms.

Non-operative treatment group:

This treatment pathway will comprise fluid resuscitation, minimum of 24 hours broad spectrum Intravenous (IV) antibiotics (per local policies), minimum of 12 hours nil by mouth (NBM) and regular clinical review to detect signs and symptoms of significant clinical deterioration including, but not limited to, increasing fever, increasing tachycardia, and increasing tenderness. After the initial 12-hour period of NBM, oral intake will be advanced as tolerated. Children successfully treated without an operation, will be converted to oral antibiotics once they are afebrile for 24 hours and tolerating oral intake (per local policies and after the minimum 24 hours IV).

Clinical reviews will also be completed at approximately 24 and 48 hours post randomisation. Any children who show signs of significant clinical deterioration by 24 hours, or at any point during the trial, will undergo appendicectomy. Children who are considered stable or improving will continue with non-operative treatment. At 48 hours, any children who have not shown clinical improvement will also undergo appendicectomy. The decision to continue non-operative treatment at these time points or to recommend discontinuation of non-operative treatment and appendicectomy, will be made by the treating consultant and based on clinical judgement rather than any specific features that are not evidence based. All reasons for change in treatment will be recorded in detail.

Any children who receive an appendicectomy for an incomplete response to non-operative treatment, will follow a standardised post-operative treatment regime already in use at each institution and identical to that used in the appendicectomy arm. The reason for having an appendicectomy will be recorded.

Appendicectomy group:

Children randomised to the appendicectomy arm will undergo either open or laparoscopic appendicectomy at the surgeon's discretion, performed by a suitably experienced trainee (as per

routine current practice) or a consultant. A peritoneal microbiology swab will be taken at the time the peritoneum is first opened or from the appendix, and any peritoneal fluid sent for microbiological culture. The results of this swab will be recorded.

Patients will receive IV antibiotics from the time of randomisation and be treated post-operatively with IV antibiotics according to existing institutional protocols, however the following recommended regime is used to guide practice: children with acute uncomplicated appendicitis or a macroscopically normal appendix will receive no further antibiotics. Children with a perforated appendix (defined as a faecolith or faecal matter within the peritoneal cavity, or visualisation of a hole in the appendix) will continue to receive IV antibiotics for a minimum of 3 days, and will receive a minimum total course of antibiotics of 5 days (IV and oral). It is not possible to standardise the duration of antibiotics therapy due to anticipated variation in intra-operative findings and in response to treatment. The type of antibiotics used will be identical to those used in the non-operative treatment arm within each centre. 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 the 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.

Discharge Assessment:

Criteria for discharge home will be identical to those in both treatment groups and will be: vital signs within normal limits for age, afebrile for ≥24 hours, tolerating light diet orally, adequate oral pain relief and be mobile. Patients will receive a total course of 10 days antibiotics following randomisation, unless decided otherwise by the clinician. If more than 10 days oral antibiotics are administered, this will be recorded (including reason). Children who receive non-operative treatment will not be

routinely offered interval appendicectomy but will be counselled about the risk of recurrence using best available data.

Once a decision to discharge the child has been made, a member of the clinical team who has not been directly involved in the child's treatment will be asked to complete a discharge assessment. This assessor will not have prior knowledge of the randomisation or treatment received by the child. Upon completion of the discharge assessment, they will "guess" which treatment the child received. If the assessor should become unblinded during the assessment, this will also be recorded. Through this we hope to be able to determine the feasibility of a blinded discharge assessment in a future RCT.

Follow up:

Follow-up appointments for all participants will take place at 6 weeks, 3 and 6 months following discharge, either in the outpatient clinic or the Clinical Research Facility at each centre. If a face-to-face appointment is not possible, the 3 and 6 month follow up can be completed over the phone. Data on resource use, time to return to daily activities and recurrent appendix-related problems (including unexplained abdominal pain and recurrence) will be collected prospectively to ensure high accuracy. The schedule of enrolment, intervention and follow up can be found in figure2.

Figure 2: Patient schedule of procedures (SPIRIT).

Primary outcome:

The primary outcome is to assess whether it is feasible to conduct a multi-centre RCT testing the effectiveness and cost-effectiveness of a non-operative treatment pathway for the treatment of acute uncomplicated appendicitis in children. This will be evaluated as the proportion of eligible patients who are approached and recruited to the study over 12 months.

Secondary outcomes:

The secondary outcomes are predominately centred on the qualitative and COS sub studies contributing towards the development of a future RCT.

1. Willingness of parents, children and surgeons to take part in a randomised study comparing operative versus non-operative treatment and identify anticipated recruitment rate. This will be assessed from audio recorded family-surgeon recruitment consultations, interviews with patients, parents, surgeons and nurses, surgeon surveys and focus groups.
2. Identification of strategies to optimise surgeon-family communication using the above consultation and interview data.
3. Design of a future RCT from the perspectives of stakeholders at participating sites (children, parents, surgeons, nurses etc.) informed by the consultation and interview data, surgeon surveys and focus groups.
4. Assessment of the equipoise and willingness of UK paediatric surgeons to participate in a future RCT through surgeon surveys and focus groups.
5. Clinical outcomes of trial treatment pathways including (i) overall success of initial non-operative treatment (measured as the number of patients randomised to non-operative treatment, discharged from hospital without appendicectomy); (ii) complications of disease and treatment (measured during hospital stay and 6 month follow-up period); (iii) rate of recurrent appendicitis during 6 month follow-up period.
6. Performance of study procedures including retention of participants for the duration of the study, and feasibility of outcome recording and data collection systems.

Sample Size Calculations:

The study will recruit participants from 3 centres for 12 months. Each centre treats 80-100 children per year with acute appendicitis, with an estimate that at least 130 will be eligible out of the 240-300 potential patients. Assuming 40-50% will be recruited (i.e. 52-65 participants in feasibility RCT) we will be able to estimate a true 40% recruitment rate with a 95% confidence interval (CI) of 31% to 49% and a true 50% recruitment rate with a 95% CI of 41% to 59%. 52-65 participants in the feasibility RCT will be adequate to test treatment pathway procedures, data collection methods and loss to follow-up.

For the embedded qualitative work related to recruitment, we will recruit until we reach data saturation which we estimate will entail analysing approximately 40 recruitment consultations, 20-30 family interviews, and 20-25 healthcare professional interviews.

Clinical trial data analysis:

Data analysis will be performed by the study statistician who will be blinded to treatment allocation by the use of coded data, as per the statistical analysis plan. As this is a feasibility study, all analyses will be treated as preliminary and exploratory and will be mainly descriptive. Feasibility outcomes (number of eligible patients, recruitment/retention rates, reasons for non-participation, success of blinding of the discharge assessor), treatment outcomes and complications will be presented by simple summary statistics with 95% confidence intervals. Clinical outcome measures will be compared between treatment groups in an exploratory analysis, and variability estimates will be used to inform the sample size for a future definitive trial. The study will be reported in accordance with the CONSORT 2010 statement.

Trial Oversight and Safety Monitoring:

A Study Management Group (SMG) will be responsible for overseeing the day-to-day management of the trial. A Trial Steering Committee (TSC) and Data Monitoring and Safety Committee (DMSC) will also share independent oversight of the study. The DMSC will review the trial and its data from a safety and ethical perspective and will make recommendations regarding the continuation of the trial to the TSC who will make the ultimate decision. The roles and responsibilities of each committee is detailed in a separate charter. The SMG will feed back to the SSAG, and vice versa.

Any patient who does not complete the non-operative treatment pathway within the trial (i.e. deteriorates or does not improve) and undergoes appendicectomy will be reported to the Trial Manager (TM) within 48 hours of appendicectomy. The TM will inform the TSC chairperson and convey the clinical data relating to this patient. The TSC chair will hold responsibility for determining whether to ask the DMSC to meet and review the data from that patient. The DMSC will subsequently advise

the TSC on their findings including an assessment of whether it is acceptable to continue to recruit patients.

2. Qualitative Sub Study:

The embedded qualitative sub-study comprises audio recordings of recruitment consultations between patients, their families and recruiters (paediatric surgeons and research nurses), and follow up interviews with patients, their families and recruiters about their experiences of recruitment and the trial. Focus groups will also be conducted with paediatric surgeons at non-study sites about their views of the trial. When patients are approached about the study, they will be asked for verbal consent to audio record the discussion. Seeking written consent for the audio recording at this point would distract from the focus of the consultation, therefore we will ask patients at the end of the consultation for written consent to keep the recording and use it for analysis. After discharge a trained qualitative researcher will contact and invite patients and families to be interviewed either in their homes or by telephone. Recruiters will also be invited to be interviewed either in their place of work or by telephone. All consultations and interviews will be digitally audio-recorded and uploaded for transcription by a professional transcription service and pseudo anonymised before analysis.

Analysis of recruitment consultations:

Analyses of the recruitment consultations will use both the recordings and transcripts to document the interactions between recruiters and families, explore information provision, use of communication techniques as well as intervention preferences and trial participation decisions. If analyses of the audio-recordings suggest that recruitment difficulties are potentially linked to communication during the recruitment consultation, this will be fed back to the local PIs so training of recruiters can be implemented immediately. The equipoise and views of health care professionals recruiting to the trial will also be assessed, as well as the key ways in which their views differ from non-participating surgeons.

The analyses will also draw upon content analytic methods to describe what was said by whom and how often in the audio-recordings of recruitment sessions. Constant comparison methods will also inform identification of common or divergent themes, particularly focusing on the impact of statements by the recruiter on parent responses and views. This will focus on key sections of the transcripts, for example, when randomisation is offered. The percentage of eligible patients recruited will be documented using site screening logs, noting any families who decline randomisation or do not accept the randomised allocation.

Analysis of interview and focus group data:

The findings from the analysis of the recruitment consultations will be linked with qualitative data from the interviews where patients discuss the acceptability of trial methodology to determine the feasibility and acceptability of a full trial, and also with the recruiter interviews. Analysis of interview and focus group data will draw on the principles of the constant comparative method and thematic analysis. One member of the research team will lead a process of 'cycling' between the developing analysis and new data. Other members of the qualitative study team (including at least one surgeon) will develop and test the analysis by periodic discussion and independent analyses of a proportion of transcripts to compare coding and findings.

Initially, each transcript will be read several times by the lead analyst, before developing open codes to describe each relevant unit of meaning, although coding will occur at multiple levels, from detailed descriptions of communication and experiences of the trial, to the general orientation of participants towards clinical research. Through comparison within and across the transcripts, the open codes will be developed into categories to reflect and test the developing analysis. The categories will be organised into a framework to code and index the transcripts using QSR NVivo software. The framework categories will be continually checked and modified to ensure an adequate 'fit' with the data, whilst also accounting for variation in the data and 'deviant' cases. A second member of the

team will check the categories and the assignment of data to them. Our analytic approach will be informed by writings on quality in qualitative research [30].

5. Patient and Public Involvement

We recognise that PPI is a crucial element for this study, and as such, will form a SSAG made up of parents, children and young people; some of which will have experience of treatment for acute, uncomplicated appendicitis. This group will provide overarching consultation and collaboration functions for the programme of research, minus the HE sub-study. The group will help devise patient and parent documentation (including but not limited to, information sheets, consent forms, and a recruitment video), provide insight on the qualitative sub-study interview schedule and COS development. They will also help with the dissemination of the results; back to study participants, via information sources accessed by children, young people and parents, and through a variety of media.

Discussion

Progression to main trial:

Through this initial study we aim to inform the design, conduct and feasibility of a future efficacy RCT whilst confirming the safety of non-operative treatment in UK paediatric surgical centres for the first time. The decision to progress to a future RCT will be based on a combination of recruitment rate achieved, safety of non-operative treatment and adequate surgeon interest. These issues will be discussed by the trial management and oversight groups and be reviewed by a new funding panel. Currently we think that a future main RCT will be considered feasible if:

1. The lower boundary of the 95% CI of the recruitment rate is above 20%. Whilst it is likely there are adequate patients to complete a study in which the recruitment rate is less than 20%, this is interpreted as lack of patient interest in non-operative treatment or potentially concerns about the trial and associated treatment.
2. The DMSC do not stop the trial on safety grounds. If the DMSC choose to stop the trial, the non-operative treatment pathway will have to be reconsidered before a future RCT is planned.

3. Adequate surgeons and centres can be identified are required to achieve target recruitment. Based on the current sample size estimate, 5-10 UK Paediatric Surgery Centres are required to make a future RCT feasible.

Specific Ethical Considerations:

1. Participants will be randomised to a novel care pathway, which although in use at a number of institutions worldwide, has not been rigorously tested to assess efficacy and safety in participating centres. Although existing literature proposes that the non-operative pathway is safe [7, 16, 24], patients and their families will be informed that the clinical outcomes are being investigated as part of the study. Clinical reviews have been incorporated into the treatment pathways to minimise risk and/or complications of unsuccessful treatment.
2. Although written informed consent will be given by the parent or guardian, the child will be given age appropriate information about the study and may confirm their assent during the completion of the consent form if they wish to do so. Consent will be taken by a member of the surgical team who has experience recruiting children to research and completed appropriate Good Clinical Practice training. A copy of the study consent form is included with the study protocol [see additional file 1]
3. Due to the urgency associated with the treatment of appendicitis, the period for taking consent will be short to ensure that the research process does not impede upon the provision of safe and effective care but does allow sufficient time for patients and their family to make an informed decision about the trial.

Some patients/parents may be concerned that delay in appendicectomy may increase the rate of perforation and AEs. However this is not borne out by the literature on large numbers of adult [31] and paediatric patients [31-35] and participants will be counselled accordingly.

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

Trial Status

Protocol version 2, 10th April 2017. The study opened to recruitment on the 1st March 2017 and will recruit patients for a period of 12 months until 28th February 2018 at 3 paediatric surgical teaching hospitals in England; Alder Hey Children's Hospital, Liverpool, Southampton General and St George's Hospital, London.

List of Abbreviations

AE	Adverse Event
CI	Confidence Interval
COS	Core Outcome Set
DMSC	Data Monitoring and Safety Committee
HE	Health Economics
IV	Intravenous
NBM	Nil By Mouth
NIHR	National Institute of Health Research
NHS	National Health Service
PPI	Patient and Public Involvement
RCT	Randomised Controlled Trial
SMG	Study Management Group
SSAG	Study Specific Advisory Group
TM	Trial Manager

TSC	Trial Steering Committee
UK	United Kingdom

Declarations

Ethics approval and consent to participate:

Approval for this study was granted by the South Central – Hampshire A Research Ethics Committee (16/SC/0596) and written informed consent will be obtained from the parents/guardians of the patients before any trial procedures are completed. There is also the option for the patients to confirm their assent during the completion of the consent form.

Consent for publication:

Not applicable

Availability of data and material:

Not applicable

Competing interests:

Professor Jane Blazeby is a NIHR Senior Investigator.

The remaining authors report no competing interests.

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NH and NJH developed the first draft of the manuscript in accordance with the SPIRIT checklist [see Additional file 2]. BY, FS and LB composed the Qualitative Sub Study section and EW drafted the PPI section. All authors reviewed and approved the final manuscript.

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References

1. St Peter, S.D., et al., *Single daily dosing ceftriaxone and metronidazole vs standard triple antibiotic regimen for perforated appendicitis in children: a prospective randomized trial.* J Pediatr Surg, 2008. **43**(6): p. 981-5.
2. Minneci, P.C., et al., *Effectiveness of Patient Choice in Nonoperative vs Surgical Management of Pediatric Uncomplicated Acute Appendicitis.* JAMA Surg, 2015: p. 1-8.
3. Varadhan, K.K., K.R. Neal, and D.N. Lobo, *Safety and efficacy of antibiotics compared with appendicectomy for treatment of uncomplicated acute appendicitis: meta-analysis of randomised controlled trials.* BMJ : British Medical Journal, 2012. **344**.
4. Lee, S.L., et al., *Does age affect the outcomes and management of pediatric appendicitis?* J Pediatr Surg, 2011. **46**(12): p. 2342-5.
5. Mizrahi, I., et al., *Comparison of pediatric appendectomy outcomes between pediatric surgeons and general surgery residents.* J Surg Res, 2013. **180**(2): p. 185-90.
6. Tiboni S, B.A., Hall NJ, *Outcome of appendicectomy in children performed in paediatric surgery units compared with general surgery units.* Br J Surg, 2014. **101**(6): p. 707-714.
7. Georgiou, R., et al., *Efficacy and Safety of Nonoperative Treatment for Acute Appendicitis: A Meta-analysis.* Pediatrics, 2017. **139**(3).
8. Bowers, W.F., C.W. Hughes, and K.B. Bonilla, *The treatment of acute appendicitis under suboptimal conditions.* U S Armed Forces Med J, 1958. **9**(11): p. 1545-57.
9. Vons, C., et al., *Amoxicillin plus clavulanic acid versus appendicectomy for treatment of acute uncomplicated appendicitis: an open-label, non-inferiority, randomised controlled trial.* Lancet, 2011. **377**(9777): p. 1573-1579.
10. Styrud, J., et al., *Appendectomy versus antibiotic treatment in acute appendicitis. a prospective multicenter randomized controlled trial.* World J Surg, 2006. **30**(6): p. 1033-1037.
11. Hansson, J., et al., *Randomized clinical trial of antibiotic therapy versus appendicectomy as primary treatment of acute appendicitis in unselected patients.* Br J Surg, 2009. **96**(5): p. 473-481.
12. Eriksson, S. and L. Granstrom, *Randomized controlled trial of appendicectomy versus antibiotic therapy for acute appendicitis.* Br J Surg, 1995. **82**(2): p. 166-169.
13. Mason, R.J., *Surgery for appendicitis: is it necessary?* Surg Infect (Larchmt), 2008. **9**(4): p. 481-8.
14. Ansaloni, L., et al., *Surgery versus conservative antibiotic treatment in acute appendicitis: a systematic review and meta-analysis of randomized controlled trials.* Dig Surg, 2011. **28**(3): p. 210-21.
15. Liu, K. and L. Fogg, *Use of antibiotics alone for treatment of uncomplicated acute appendicitis: a systematic review and meta-analysis.* Surgery, 2011. **150**(4): p. 673-683.
16. Minneci, P.C., et al., *Feasibility of a nonoperative management strategy for uncomplicated acute appendicitis in children.* J Am Coll Surg, 2014. **219**(2): p. 272-9.
17. Gorter, R.R., et al., *Initial antibiotic treatment for acute simple appendicitis in children is safe: Short-term results from a multicenter, prospective cohort study.* Surgery, 2015. **157**(5): p. 916-23.
18. Svensson, J.F., et al., *Nonoperative treatment with antibiotics versus surgery for acute nonperforated appendicitis in children: a pilot randomized controlled trial.* Ann Surg, 2015. **261**(1): p. 67-71.
19. Barsness, K.A., et al., *IL-1beta induces an exaggerated pro- and anti-inflammatory response in peritoneal macrophages of children compared with adults.* Pediatr Surg Int, 2004. **20**(4): p. 238-42.
20. Barsness, K.A., et al., *Endotoxin induces an exaggerated interleukin-10 response in peritoneal macrophages of children compared with adults.* J Pediatr Surg, 2004. **39**(6): p. 912-5; discussion 912-5.

21. Dimmitt, R.A., et al., *Salvage laparotomy for failure of peritoneal drainage in necrotizing enterocolitis in infants with extremely low birth weight.* J Pediatr Surg, 2000. **35**(6): p. 856-859.
22. Abes, M., B. Petik, and S. Kazil, *Nonoperative treatment of acute appendicitis in children.* J Pediatr Surg, 2007. **42**(8): p. 1439-42.
23. Armstrong, J., et al., *Non-operative management of early, acute appendicitis in children: is it safe and effective?* J Pediatr Surg, 2014. **49**(5): p. 782-5.
24. Steiner, Z., et al., *A role for conservative antibiotic treatment in early appendicitis in children.* J Pediatr Surg, 2015. **50**(9): p. 1566-8.
25. Turhan, A.N., et al., *Comparison of operative and non operative management of acute appendicitis.* Ulus Travma Acil Cerrahi Derg, 2009. **15**(5): p. 459-62.
26. Hall, N.J., et al., *Appendectomy versus non-operative treatment for acute uncomplicated appendicitis in children: study protocol for a multicentre, open-label, non-inferiority, randomised controlled trial.* BMJ Paediatrics Open, 2017. **1**(1).
27. Xu, J., et al., *Acute uncomplicated appendicitis study: rationale and protocol for a multicentre, prospective randomised controlled non-inferiority study to evaluate the safety and effectiveness of non-operative management in children with acute uncomplicated appendicitis.* BMJ Open, 2016. **6**(12): p. e013299.
28. Folaranmi, S.E., et al., *Variation in provision and outcome of emergency appendicectomy in paediatric specialist centres.* Bulletin of The Royal College of Surgeons of England, 2014. **96**(10): p. 9-14.
29. Sherratt, F.C., et al., *Development of a core outcome set to determine the overall treatment success of acute uncomplicated appendicitis in children: a study protocol.* BMJ Paediatrics Open, 2017. **1**(1).
30. Mays, N. and C. Pope, *Qualitative research in health care. Assessing quality in qualitative research.* BMJ, 2000. **320**(7226): p. 50-52.
31. Bhangu, A., *Safety of short, in-hospital delays before surgery for acute appendicitis: multicentre cohort study, systematic review, and meta-analysis.* Ann Surg, 2014. **259**(5): p. 894-903.
32. Serres, S.K., et al., *Time to appendectomy and risk of complicated appendicitis and adverse outcomes in children.* JAMA Pediatrics, 2017.
33. Ingraham, A.M., et al., *Effect of delay to operation on outcomes in adults with acute appendicitis.* Arch Surg, 2010. **145**(9): p. 886-92.
34. Drake, F.T., et al., *Time to appendectomy and risk of perforation in acute appendicitis.* JAMA Surg, 2014. **149**(8): p. 837-44.
35. Hornby, S.T., et al., *Delay to surgery does not influence the pathological outcome of acute appendicitis.* Scand J Surg, 2014. **103**(1): p. 5-11.

Additional files

Figure 1:

Figure1.docx, Clinical pathway for both treatment arms

Figure 2:

Figure2.doc, Patient schedule of procedures (SPIRIT).

Additional file 1:

Additional file 1.doc, Parental Consent form with optional patient assent

Additional file 2:

Additional file 2.doc, SPIRIT Checklist