Conservative treatment for uncomplicated appendicitis in children: the CONTRACT feasibility study, including feasibility RCT

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Scientific summary

The CONTRACT feasibility study, including feasibility RCT

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Scientific summary

Appendicitis is the most common surgical emergency in children. Currently, the routine treatment for children with acute appendicitis in the UK is an appendicectomy. However, there is increasing interest and research into non-operative treatment of appendicitis in adults and children.

Although appendicectomy is usually a simple procedure, it requires a general anaesthetic and an abdominal operation, with inherent risks of surgical complications and other long-term sequelae. Wound infection and intra-abdominal abscess are both well-recognised complications, and there is a risk of hospital re-admission. Overall, in children with appendicitis, the risk of one or more of these complications is about 15%. Furthermore, about 10% of children who undergo appendicectomy do not actually have acute appendicitis and could be considered to have had an unnecessary operation.

The financial and logistic burden of paediatric appendicitis is huge. In England, treatment of appendicitis costs in excess of £21M per year. Appendicectomy requires significant resource use, including need for out-of-hours surgery (45% of all paediatric appendicectomies are performed between 18.00 and 08.00).

There is growing scientific and clinical interest in the use of non-operative treatment with antibiotics; a number of reports suggest that this is a safe and effective approach in selected children. There are a number of potential benefits to non-operative treatment, including avoiding the trauma, physiological stress, psychological distress and physical scarring of an operation; avoiding complications as a result of surgery or general anaesthesia; and reducing NHS resource use with potential for significant savings if non-operative treatment is effective (> £500 per case, based on the Healthcare Resource Group tariff).

However, we do not yet know how the outcomes of non-operative treatment compare with those of appendicectomy. In particular, we need to understand, in the UK setting, the safety and efficacy of non-operative treatment compared with appendicectomy, and the risk of recurrent appendicitis following successful non-operative treatment.

Although some studies have investigated non-operative treatment of appendicitis in adults, this research cannot be applied to children because of pathophysiological differences. Our aim is to perform a UK-based multicentre randomised controlled trial to test the clinical effectiveness and cost-effectiveness of non-operative treatment of uncomplicated acute appendicitis in children, compared with appendicectomy. Owing to perceived challenges in performing such a trial, we first planned this study to assess feasibility.

Objectives

Overarching aim

The main aim was to assess the feasibility of conducting a multicentre randomised controlled trial testing the clinical effectiveness and cost-effectiveness of a non-operative treatment pathway for the treatment of uncomplicated acute appendicitis in children.

Specific objectives

- Assess the willingness of parents and children to be enrolled in, and surgeons to recruit to, a randomised trial comparing operative with non-operative treatment, and identify the anticipated recruitment rate.
- Identify strategies to optimise surgeon–family communication to inform the future randomised controlled trial.
- Enhance the design of a future randomised controlled trial from the perspectives of stakeholders at participating sites (children, parents, surgeons and nurses).

- Identify what core outcomes family members and surgeons regard as important to measure in a future randomised controlled trial and develop a core outcome set.
- Assess the equipoise and willingness of UK paediatric surgeons to participate in a future randomised controlled trial.
- Generate data to allow for the design of a definitive randomised controlled trial, including sample size calculation and identification of key cost drivers and other parameters necessary to perform a full economic analysis.
- Examine the clinical outcomes of children with acute appendicitis who received non-operative treatment, including an initial assessment of the efficacy and safety of this treatment pathway in our centres.
- Ensure that the entire research programme is well informed by a group of children and parents.

Methods

A mixed-methods feasibility study was designed to meet these objectives, comprising the following:

- A three-centre randomised controlled feasibility trial conducted over 12 months comparing emergency appendicectomy with non-operative treatment in children with uncomplicated acute appendicitis. Children (aged 4–15 years) with a clinical ± radiological diagnosis of uncomplicated acute appendicitis, but not suspected to have more advanced disease, were randomised (1 : 1 ratio) to undergo appendicectomy or to receive a non-operative treatment pathway. This pathway comprised broad-spectrum antibiotics with close clinical observation; antibiotics were given intravenously (for a minimum of 24 hours), followed by orally, to complete a total 10-day course. Children who deteriorated or who did not respond by 48 hours underwent appendicectomy according to predefined criteria. Discharge criteria for both treatment arms were identical. Complications in both treatment arms were treated as clinically appropriate; recurrent appendicitis was treated with appendicectomy. Follow-up was for 6 months after randomisation.
- Embedded qualitative research to facilitate optimisation of recruitment to the feasibility randomised controlled trial, and the design and conduct of a future randomised controlled trial. A sample of trial recruitment consultations ($n = 58$) and semistructured interviews with health professionals ($n = 35$) and families ($n = 28$), including those who participated in and those who declined participation in the trial, were audio-recorded and analysed qualitatively. The findings informed ongoing training for recruiters on communication with families. This training was delivered throughout the trial at recruiting sites. Trial protocol changes were made in accordance with findings from the qualitative study.
- A health economics substudy to determine the feasibility of, and inform the design of, a cost-effectiveness analysis alongside a future effectiveness trial. We assessed different data collection methods and tools to explore whether or not reliable health service use data can be obtained from hospital clinical records (microcosting) and patient reports of resource use. We compared costs arising from microcosting and macrocosting approaches. We also compared two routinely used health-related quality-of-life instruments to determine their sensitivity to detect changes in quality of life in each trial treatment arm over time.
- Development of a core outcome set for the treatment of children and young people with uncomplicated acute appendicitis. Individuals who were children or young people who had previously received treatment for acute appendicitis, parents of children or young people who had previously received treatment for acute appendicitis, or specialist paediatric surgeons or adult general surgeons who treat children with appendicitis were invited to participate in a consensus process comprising a three-phase Delphi process (administered online), followed by two consensus meetings. Initial outcomes were selected from a systematic review of the existing literature, and a standard scoring system was used to assess the importance of each outcome during the consensus process.
- An online survey of UK-based paediatric surgeons was undertaken to understand their attitudes and equipoise to the research question, to assess their willingness to participate in a future randomised controlled trial and to understand barriers to and facilitators of their participation.

- A detailed programme of patient and public involvement underpinned all study activities, with the aim of optimising the acceptability and relevance of the study to potential participants and their families.

Results

In the feasibility randomised controlled trial, 275 children with acute appendicitis were screened for inclusion, of whom 131 met the eligibility criteria; of these, 115 were approached to participate. Of those approached, 57 (50%, 95% confidence interval 40% to 59%) agreed to participate and were enrolled. The median age was 10.5 years (range 4.9–15.5 years), and 36 (63%) were boys. Nearly half of all participants (27/57) were recruited out of hours (i.e. between 18.00 and 08.00) and > 21 different surgeons were involved in recruitment consultations. Three participants (5%) withdrew trial consent after randomisation and one was lost to follow-up. Follow-up appointments were completed by 48 out of 54 (89%) participants at 6 weeks, by 46 out of 54 (85%) participants at 3 months and by 45 out of 53 (85%) participants at 6 months. A £10 voucher offered part-way through the study to incentivise follow-up attendance increased attendance from 83% to 100% at 3 months and from 83% to 89% at 6 months.

Of the 28 participants randomised to appendicectomy, 27 received the intervention. Seventeen were found to have uncomplicated acute appendicitis, but eight had perforated appendicitis and two had a histologically normal appendix. The median length of stay in hospital was 65 (range 20–196) hours after randomisation. Three children (11%) were re-admitted to hospital, following initial discharge, for investigation and/or treatment of potential complications related to appendicectomy. All were treated with intravenous antibiotics and one received percutaneous abscess drainage. Two further children received oral antibiotics for a wound infection.

Of the 29 participants randomised to non-operative treatment, 27 received the intervention. Nineteen (70%) of these participants responded to initial non-operative treatment and were discharged home a median of 61 (range 34–125) hours following randomisation. The remaining eight underwent appendicectomy during initial hospital admission because of parental choice (withdrawal from treatment allocation, $n = 1$), clinical deterioration ($n = 6$) and no improvement at 48 hours ($n = 1$). Among these eight, four had simple acute appendicitis and four had perforated appendicitis. Among the 19 participants who initially responded to non-operative treatment, seven developed recurrent appendicitis after hospital discharge and underwent appendicectomy.

The embedded qualitative research identified several barriers to recruitment, including imbalance in how surgeons initially presented the treatment arms, and surgeon and family treatment preferences. Families who were less willing to consider non-operative treatment were less willing to participate in the trial. Parents who declined to participate often described concerns about non-operative treatment failure and appendicitis recurrence. Parents with previous experience of perforated or complicated appendicitis were more likely to favour appendicectomy and were less likely to participate. Parents' and patients' treatment preferences often diverged. In training sessions informed by the qualitative findings, we encouraged surgeons to adjust their communication to give a more balanced presentation of the treatment arms and to explore families' beliefs about antibiotics and surgery for appendicitis to address their treatment preferences. Retraining of recruiters was associated with an increase in recruitment rate over the duration of the trial to a maximum of 72% during the final 3 months. This qualitative research also identified further strategies to improve the acceptability of a future trial to participants and their families, as well as recommendations to enhance trial design and delivery.

In the health economics substudy, we demonstrated that hospital clinical records are a feasible and reliable source of data that can be integrated with research data to estimate costs, using a microcosting approach. This approach could be used to conduct economic evaluations alongside clinical studies.

We have established the characteristics and sensitivity of quality-of-life instruments in relation to treatment arms and, importantly, the effect of measuring quality of life at different time points.

The assessment of costs of both treatment pathways identified that the main cost drivers are the ward stay cost and the cost of the operation. The results also showed that the NHS reference unit cost data might not be completely accurate in cases for which a new intervention is proposed, for which no established unit cost data are available. However, for any future design of a study, these findings ought to be carefully considered against the time requirement and, hence, costs of adopting a detailed microcosting approach.

The results of assessing two frequently used health-related quality-of-life instruments showed that the timing and duration of data collection could influence the result of the cost-effectiveness analysis. This result highlights the need for analysts to use their judgement and appropriate justification in dealing with this issue when designing a definitive randomised controlled trial, as this could affect reporting the intervention as cost-effective or not. All these findings will be integral parts of the design for the future definitive randomised controlled trial, but they are also extremely important in aiding decisions regarding the design of other randomised controlled trials and in adding to discussions regarding the methodological considerations of designing and conducting economic evaluations (assessing cost-effectiveness) alongside randomised controlled trials.

For the core outcome set development, 195 participants registered for the consensus process, of whom 147 (75%) actually participated in the Delphi process; 90 participants completed all three phases. All stakeholder groups were represented in each phase of the Delphi process and at the consensus meetings. A 14-item core outcome set was successfully developed. There was a divergence of opinion between surgeons and families regarding a primary outcome for a future trial, which needs resolution.

In a survey of UK paediatric surgeons, there was broad support for the research question, with only 22% disagreeing that there is uncertainty regarding which treatment is more effective. A total of 51% of respondents indicated that they would be willing to recruit to a future effectiveness trial with an unchanged trial design. Feedback from surgeons provided considerations for improving future trial design to enhance surgeon acceptability.

A study-specific advisory group was successfully convened comprising 10 children and young people (aged 9–18 years), some of whom had had appendicitis, and four parents of children and young people who had had appendicitis. Through regular meetings and electronic communication, they successfully contributed to all aspects of this feasibility study, in particular to participant- and family-facing materials such as information sheets, information videos, interview topic guides and lay wording of medical terminology. Although we cannot empirically demonstrate the impact of the patient and public involvement, we believe that it has contributed significantly to the successful completion of this complex and challenging study.

Conclusions

We have demonstrated the feasibility of a randomised controlled trial, efficacy of our recruitment methods and efficacy and safety of our treatment and follow-up pathways. This, combined with adequate surgeon interest in a future trial, suggests that a randomised controlled trial of appendicectomy versus non-operative treatment in children with uncomplicated acute appendicitis is possible and will enable us to understand the comparative clinical effectiveness of these treatment approaches.

Further work is required to (1) improve identification of children with a secure diagnosis of uncomplicated acute appendicitis, as opposed to more advanced disease, and (2) reach agreement on the appropriate primary outcome for a future trial.

The embedded qualitative study has identified barriers to recruitment in this urgent care setting, enabling us to develop recruitment training to improve communication with families. Findings have provided lessons for improving informed consent and recruitment in a future definitive randomised controlled trial, as well as recommendations for optimising trial design and delivery.

The health economics study has demonstrated that reliable resource use data could be obtained and integrated into research data. We identified key cost drivers for both treatment pathways and assessed two paediatric quality-of-life instruments, generating essential reliable data to support the design of an economic evaluation alongside a future randomised controlled trial assessing cost-effectiveness.

We have successfully established a core outcome set that provides, for the first time, a core set of outcomes for use in future research in the field of uncomplicated acute appendicitis in children. Further work is required to determine how some of these outcomes should be measured and the appropriate timing of measurement.

We believe that the patient and public involvement programme has been extremely effective; we have successfully engaged with a multigenerational group that has contributed positively to a wide range of study activities.

Recommendations for future research

Given the ongoing burden of treating acute appendicitis, and ongoing public and clinician interest in the role of non-operative treatment, a randomised controlled trial to establish the clinical effectiveness and cost-effectiveness of non-operative treatment versus appendicectomy in the UK remains warranted and should be performed. We recommend that a limited package of qualitative work be included in this randomised controlled trial, primarily to enable the delivery of a high-quality recruitment training programme and to optimise recruitment, with particular focus on new centres. As the design of a future randomised controlled trial will be slightly different from this feasibility randomised controlled trial, and we will recruit in a larger number of centres, we recommend that the future randomised controlled trial has an internal pilot phase with clear progression criteria.

Prior to this, additional work should be undertaken to determine a reliable pathway to identify those children who have uncomplicated acute appendicitis, as opposed to more advanced disease. Crucially, this should not involve the use of diagnostic imaging, as a pathway that includes imaging would be a major deviation from current routine practice in the UK and would have major cost implications. Such a pathway is unlikely to be acceptable to clinicians and the results would not be generalisable to all UK centres.

During the design phase of the future trial, consensus should be reached among relevant stakeholder groups regarding the appropriate primary outcome for the trial and the effect size to be investigated. The trial should aim to measure and report all outcomes included in the core outcome set.

We recommend our patient and public involvement approach to other studies in the future.

Trial registration

This trial is registered as ISRCTN15830435.

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This report

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