

# Active observation versus interval appendicectomy following successful non-operative treatment of appendix mass in children: a randomised controlled evaluation

Nigel J Hall PhD<sup>1,2</sup>, Simon Eaton PhD<sup>3</sup>, Michael P Stanton MD<sup>2</sup>, Agostino Pierro FRCS<sup>4</sup>, David M Burge FRCS<sup>2</sup> on behalf of the CHINA study collaborators and the Paediatric Surgery Trainees Research Network

1. University Surgery Unit, Faculty of Medicine, University of Southampton, Southampton, UK
2. Department of Paediatric Surgery and Urology, Southampton Children's Hospital, Southampton, UK
3. Developmental Biology and Cancer Programme, UCL Great Ormond Street Institute of Child Health, London, UK
4. Division of General and Thoracic Surgery, The Hospital for Sick Children, Toronto, Canada

## Corresponding author

Nigel J Hall

Faculty of Medicine, University of Southampton, Mailpoint 816, Southampton General Hospital, Tremona Road, Southampton SO16 6YD UK

Tel: 023 8120 6146 / 6677; Email [n.j.hall@soton.ac.uk](mailto:n.j.hall@soton.ac.uk)

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## **Abstract**

*Background:* Despite a lack of supporting evidence, most surgeons recommend routine interval appendicectomy following successful non-operative treatment of an appendix mass in children. We aimed to compare routine interval appendicectomy with active observation.

*Methods:* We did a multicentre randomised controlled study between June 2011 and December 2014 at 21 specialist paediatric surgery centres. 106 children aged 3-15 years were assigned by weighted minimization to interval appendicectomy (n=52) or active observation (n=54) with minimisation for age, trial centre, gender and presence of a faecolith on imaging. Only children who presented with an appendix mass and were successfully treated without appendicectomy or other surgical intervention were eligible. Due to the nature of the interventions blinding was not possible. Primary outcome was incidence of histologically proven recurrent acute appendicitis (active observation group) and incidence of significant complications related to interval appendicectomy. Data were analysed on an intention to treat basis. The study is registered with ISRCTN (number 93815412).

*Findings:* Incidence of histologically proven recurrent acute appendicitis in children under active observation was 12%, [95%CI 5, 23]. Incidence of significant complications related to interval appendicectomy was 6% [95%CI 1, 17%]. In the active observation group total 23% of children underwent appendicectomy within 1 year of enrolment. Time in hospital, time away from daily activities and cost were all lower with active observation than routine interval appendicectomy.

*Interpretation:* These high quality data will allow clinicians, parents and children to make an evidence-based decision regarding the justification for interval appendicectomy.

*Funding:* the BUPA Foundation.

## Background

Acute appendicitis is the most common surgical emergency in children. The lifetime risk of developing appendicitis is 7-8% with a peak incidence in the second decade of life.<sup>1</sup> Approximately 9% of children with acute appendicitis present with a palpable, fixed, walled-off mass surrounding the inflamed appendix known as an appendix mass (AM).<sup>2</sup> Treatment of the acute phase of AM in children is usually non-operative with broad spectrum intravenous antibiotics as the risk of complications from attempted appendicectomy in the presence of an inflammatory mass is high.<sup>3</sup> Following successful non-operative treatment, current surgical dogma is that interval appendicectomy (IA) should be performed in order to avoid future recurrence of acute appendicitis. However this approach has been questioned in both the paediatric<sup>4</sup> and adult literature.<sup>5</sup>

When considering whether to perform interval appendicectomy or not in this clinical scenario, clinicians and parents must balance risks and benefits related to each management option. The main factors that contribute to the decision making process related to interval appendicectomy are the incidence of recurrent acute appendicitis following successful conservative treatment of appendix mass, the morbidity and risks associated with interval appendicectomy, the risk of missing an alternative diagnosis (such as carcinoid tumour) by not performing an interval appendicectomy, and the cost effectiveness of each method of treatment. Proponents of IA argue that the risk of recurrent appendicitis is high and that interval appendicectomy is safe, and has a low morbidity. Those who opt for conservative management cite the opposite: a relatively low incidence of recurrent appendicitis and avoidable morbidity, hospital stay and cost associated with IA. A survey of UK based paediatric surgeons in 2009 reported that 68% routinely recommend IA for all children.<sup>6</sup>

Our systematic review of the available literature, published in 2011<sup>7</sup>, estimated the risk of developing recurrent acute appendicitis following successful non-operative treatment of an appendix mass in children as 20%, and the incidence of complications after IA as 3%. A key finding of this review was the limited number of published studies, the majority of which were retrospective and of relatively poor methodological quality. Only three studies contributed data to the outcome of recurrent appendicitis,<sup>8-10</sup> one of which suggested that the incidence of recurrent appendicitis was higher in children with a faecolith.<sup>9</sup>

In order to determine if IA is justified we designed the CHildren's INterval Appendicectomy (CHINA) study. This prospective, multicentre, randomised study aimed to generate high quality prospective data to allow clinicians, parents and patients to make an informed decision about the need for, and cost effectiveness of interval appendicectomy following successful non-operative treatment of appendix mass in children.

## Methods

### Study design

We performed a prospective, multicentre randomised study in which children who had had an appendix mass successfully treated non-operatively were allocated by weighted minimization to either routine interval appendicectomy or 1 year of active observation. Recruiting centres were 21 specialist Paediatric Surgery Centres. Nineteen of these centres were in the United Kingdom, one in Sweden and one in New Zealand. Ethical approval was obtained in all centres prior to recruitment. The study was performed according to a single protocol. The study was registered with the ISRCTN registry in July 2011 (identifier 93815412) and is reported in accordance with CONSORT guidelines.<sup>11</sup>

### Participants

Children (<16 years) who presented with acute appendicitis and an appendix mass were eligible for inclusion if they satisfied the following criteria: diagnosis of acute appendicitis with appendix mass; appendix mass palpable clinically, during examination under anaesthetic or identified radiologically (ultrasound or CT); have been successfully treated non-operatively during the acute stage of the illness and discharged home

Children were excluded from the study if they were aged less than 3 years at the time of initial presentation, had co-existing gastrointestinal disease (e.g. inflammatory bowel disease) or had a significant co-existing medical condition or immune defect

No formal definition of an appendix mass was used, rather the diagnosis was made by the surgeon in charge of the child's care based on any of: clinical examination, examination under anaesthesia or imaging (ultrasound and/or CT scan). Successful non-operative treatment was defined as the child being well enough to be discharged home on oral antibiotics having not undergone surgery or attempted surgery to remove the appendix nor received percutaneous drainage of any appendix related abscess. Children under 3 years were excluded due to the difficulty in making a reliable diagnosis of appendix mass in this age group.

All participants were enrolled into the study following informed parental consent. The study was explained to the parents and child if appropriate (depending on age) with the help of a study information sheet. Separate, age specific, information sheets were provided to children aged 8-11 years and those aged 12-15 years. Children aged 12 years or over were able to provide their own consent for participation if they wished, in addition to or in place of parental consent.

### Interventions

Children were allocated to one of the following treatment groups:

1. interval appendicectomy (IA)– children were scheduled to undergo elective IA (open or laparoscopic) at a timescale determined by the operating surgeon's current practice, but with an advisory timescale of 2-3 months following randomisation. Children were reviewed

in the outpatient clinic at approximately 6 weeks following interval appendicectomy and again at 1 year following randomisation.

2. active observation (AO) – children were not scheduled for routine IA but were reviewed every 3 months in the outpatient clinic for 1 year following randomisation. Any child that developed recurrent appendicitis or who had symptoms that in the opinion of the treating clinician warranted surgery, underwent appendicectomy by either open or laparoscopic approach at the surgeon's discretion.

### Treatment allocation and masking

Participants were allocated to groups (1:1 ratio) using weighted minimisation (randomisation weighting of 4) at the time of enrolment into the study using the following criteria: gender ([male], [female]), presence of faecolith on radiological investigation ([yes], [no]), age ([3-9yrs], [10-15yrs]), and collaborating centre.

Minimisation was set up using an online computerised service provided by the University of Aberdeen, UK. This allowed for concealment of previously allocated patients from all site investigators prior to allocation by minimization. Due to the nature of the interventions blinding was not possible. We included collaborating centre as one of the minimisation criteria to account for differences that may have existed in treatment approach between centres. We did not include individual surgeon as a minimisation criterion since the actual number of participants expected to be operated on by each individual surgeon was very low (less than 1 patient per surgeon where each surgeon from each participating centre was considered). Thus it is highly unlikely that treatment by any individual surgeon would influence study results.

### Outcomes

Due to the different nature of the interventions in each treatment group the primary outcomes for each group were different. All outcomes were defined *a priori*.

The primary outcome in the IA group was the incidence of significant complications during or following IA. Significant complication was defined as any complication requiring additional or unanticipated treatment including, but not limited to, intestinal perforation, haemorrhage requiring transfusion, wound infection requiring antibiotics, abscess formation, post-operative small bowel obstruction, prolonged ileus (>72hrs post-operatively). Conversion of a laparoscopic to open interval appendicectomy in the absence of another complication meeting the above definition was not defined as a significant complication.

The primary outcome in the AO group was the proportion of children developing recurrent acute appendicitis within 1 year of enrolment following successful non-operative treatment of appendix mass. Recurrent acute appendicitis was defined as appendicitis confirmed by evidence of acute inflammation on histological examination of the resected appendix or a clinical diagnosis of recurrent appendix mass in the opinion of the consultant responsible for the child's care. The presence of acute inflammation was based upon consultant histopathologist report at each individual institution.

Secondary outcomes were selected on their ability to inform the aims of the study and were relevant to one or both treatment groups including: adverse events, duration of hospital admission related to the appendix during one year after enrolment, cost of treatment related to the appendix in one year follow up, days off school / normal daily activities related to the appendix in one year follow up, details of all surgical procedures performed, histopathological evaluation of any resected appendicectomy specimen. Whilst participant safety and serious adverse events were monitored in this study, neither were included as formal study outcomes since this study compared two treatments both of which are routinely used and considered standard of care.

Data relating to all outcomes were recorded prospectively at the local centre and forwarded to the collaborating centre at completion of the study. Data related to hospital admission was recorded during or immediately following the admission. To capture data related to admission to another hospital during the 1 year follow-up period, participants were specifically asked whether they had had a hospital attendance or admission for abdominal pain or suspected appendicitis at follow-up consultations. At discharge from hospital, parents were provided with a diary card and asked to document days on which their child was unable to attend school or undertake normal daily activities during the follow-up period either due to hospital admission, recovery following hospital admission or unexplained abdominal pain.

Total length of stay during the 1 year follow-up period was calculated for all planned and unplanned hospital admissions related to the appendix or abdominal pain at any hospital.

Costs were obtained from each participating institution's finance department for the cost of running the operating theatre for 1 hour (including staff costs) during 2015 and the cost of a 24 hour period on the paediatric surgical ward during 2015. Costs from international centres were obtained in local currency and converted into UK£ using the exchange rate on 31<sup>st</sup> December 2015. Cost related to hospital admission and time in the operating theatre were calculated by multiplying these units costs by time spent in hospital and time spent in the operating theatre respectively. Hospital admission cost and theatre cost were added to give a total cost per patient during the 1 year follow-up period.

### Sample size

The study sample size was calculated to be able to demonstrate a statistically significant difference in the incidence of recurrent appendicitis between treatment groups based on of a 20% risk of recurrent acute appendicitis within the first year in the active observation group and a zero incidence in the interval appendicectomy group at 90% power. The sample size was set at 50 children in each treatment group.

### Data handling and statistical analysis

Data were collected locally by each centre and forwarded to the study coordinator at the end of the study. Data were entered into a custom designed database using Microsoft Access, exported into Microsoft Excel for handling and then analysed using statistical packages as detailed below.

All data were analysed initially on an intention-to-treat basis. Due to some crossover between groups (see study profile, Figure 1), a secondary analysis was performed based on the treatment actually received.

Primary outcomes and other categorical data are reported as incidence with 95% confidence intervals (95% CI). Continuous data are reported as median with inter-quartile range (IQR). Between-group comparisons were made using Mann-Whitney U test for univariate analyses. Multiple linear regression analysis of  $\log_{10}(\text{hours}+1)$  and  $\log_{10}(\text{cost} +1)$  transformed data was performed as data were right skewed, adjusting for age, gender, faecolith and centre. Kaplan-Meier analysis was used to calculate recurrence risk over time and the log-rank test used to compare subgroups of children. Statistical analyses and generation of figures were performed using SPSS v22 (IBM Software) and Prism v6.0 (GraphPad software);  $p < 0.05$  was considered significant.

### Study oversight

The study was overseen by a steering committee who met prior to recruitment of the first participant and regularly for the duration of the study and comprised the study co-ordinator (non-voting), two independent paediatricians and an independent paediatric surgeon, with data provided and statistically analysed by SE (not involved in clinical care). The steering committee monitored recruitment to the trial, trial conduct and reviewed any protocol violations. The steering committee mandated that an interim analysis be undertaken after half of the sample size had been recruited and followed-up for one year. This interim analysis would calculate the rate of recurrent appendicitis and if found to be over twice that anticipated (i.e. over 40%) then the study would be terminated early. This interim analysis was performed as planned and the stopping rule not found to have been met.

## RESULTS

The trial profile is shown in Figure 1. Participants were enrolled in the study between August 2011 and December 2014 with the first participant enrolled on August 8<sup>th</sup> 2011 and the final participant enrolled on December 31<sup>st</sup> 2014. The 1 year follow-up period for the final participant therefore ended on 31<sup>st</sup> December 2015. The study was open to recruitment in 21 centres with children actually enrolled in the study from 19 of these. A total of 183 children were screened and met the eligibility criteria in the recruiting centres during the study period. Of these, 106 children and/or their parents agreed to participate and were allocated to either IA or AO.

Fifty-two children were allocated to IA. Of these, two children were withdrawn from the study due to withdrawal of consent for continued participation. Of the remaining 50 children, three more declined IA but were followed-up for 1 year, two developed recurrent appendicitis prior to their planned IA and one did not receive IA within the 1 year follow-up period. Therefore a total of 44 children underwent IA during the study period. All 50 children allocated to the IA group who did not withdraw consent were analysed in the IA group on an intention to treat (ITT) basis.

Fifty-four children were allocated to the AO group. Two children became ineligible following allocated and were therefore withdrawn from the study by local investigators: one who developed a second, unrelated medical condition early during the follow-up period that required several episodes of surgery and a second who developed an intra-abdominal abscess requiring re-admission and drainage 10 days after enrolment. The remaining 52 children were analysed in the AO group on an ITT basis.

The baseline characteristics of the study groups are shown in Table 1.

Of the 50 children allocated to the IA group and included in the ITT analysis, 44 children actually received IA during the study period. IA was performed at a median 66 days after treatment allocation (IQR 51-89). Significant complications related to IA occurred in 3 children (1 port site herniation with small bowel obstruction requiring laparotomy, 2 children with wound infection requiring antibiotics). The number of children meeting the protocol definition of the primary outcome (i.e. significant complication) for the IA group was 3/50 (6% [95%CI 1, 17%]).

Of the 52 children in the AO group, 51 children received AO during the study period with a median duration of follow-up of 365 days (IQR 350-365) in those who did not undergo appendicectomy during follow-up. One child erroneously underwent IA without complications due to an administration error. Six children (12%, [95%CI 5, 23]) met the definition of primary outcome in the AO group in that they developed recurrent acute appendicitis and underwent appendicectomy with evidence of acute inflammation on histology.

Secondary outcomes are reported in accordance with the protocol and are analysed initially on an ITT basis.

In the IA group, 2 children developed recurrent appendicitis prior to their scheduled IA. One underwent laparoscopic appendicectomy, the other laparoscopic converted to open and one had a prolonged ileus (>72 hours).

Forty-four children allocated to IA actually received IA. Of these, 43 were performed using standard laparoscopy (including two conversion to open) and 1 using a single port technique. Median duration of surgery was 66 minutes (IQR 55-88) and median duration of hospital stay related to IA (not including hospitalisation for complications) was 32 hours (IQR 28-48). Twenty-seven of the 44 families returned post-discharge diary cards in whom the median time to return to school or normal daily activities after hospital discharge was 7 days (IQR 5-7). Histological reports were available for 42 of the 44 surgical specimens, all of which contained appendiceal tissue, and revealed no inflammation in 15, acute inflammation in 8, chronic inflammation in 14, fibrosis in 17 and no carcinoid tumour. Other histological findings included threadworms (n=2), lymphoid hyperplasia (n=2), eosinophilic infiltration (n=1) and granuloma (n=1) in a child who had a subsequently negative diagnostic evaluation for Crohn's disease. One minor adverse event was reported in the IA group in a child whose head was inadequately supported during anaesthesia. There was minor pain, but a satisfactory orthopaedic review and no sequelae.

In total, 12 children in the AO group underwent appendicectomy. Six of these 12 had histologically confirmed recurrent acute appendicitis (the AO group primary outcome). Hospital stay related to recurrence was 105 hours (IQR 95-140). Two children had a laparoscopic appendicectomy, one laparoscopic converted to open appendicectomy and three open appendicectomy. Post-operative complications occurred in two children: wound infection (n=1) and prolonged (>72 hours) ileus (no further surgery, n=1). At follow-up (median 87 [IQR 56-135] days after recurrence) all six children were well but one had ongoing abdominal pain with exertion and one had unsatisfactory scar cosmesis. Histology demonstrated acute appendicitis in all 6, with a faecolith seen in two (both had been positively identified on imaging at time of initial presentation with appendix mass). In one specimen, part of the Fallopian tube that had been inadvertently excised along with the appendix was identified.

During the follow-up period, a further five children in the AO group underwent appendicectomy for either suspected acute appendicitis (n=4) or ongoing abdominal pain (n=1). Histology was negative for acute inflammation in all, but revealed chronic inflammation (n=2), lymphoid hyperplasia (n=2) and serositis suggestive of an extra-appendiceal cause of inflammation (n=1). These children spent a median 50 hours in hospital (IQR 32-50) and all recovered without complication. Additionally, 5 children had a hospital admission during the follow-up period for assessment of abdominal pain, all of which resulted in discharge home without appendicectomy.

The final child in the AO who had appendicectomy had an elective IA due to an administration error.

Seven of the 12 families returned post-discharge diary cards following appendicectomy in whom the median time to return to school or normal daily activities after hospital discharge was 7 days (IQR 2-12).

Cost and total duration of hospital stay related to appendicitis within 1 year from enrolment were compared between IA and AO groups, on intention to treat basis. Summary statistics for these parameters are shown in Table 2. Active observation was associated with a significantly shorter length of hospital stay and significantly lower cost than routine IA on univariate analysis. Multiple linear regression analysis was used to determine the relationship between treatment group and these outcomes taking into account the minimisation criteria of age, gender, presence of a faecolith and centre. Results are shown in Table 3. There was no significant effect of treatment centre on either total LOS or cost (data not shown). Children allocated to receive AO spent on average 10% of

the time in hospital that those allocated to IA during the first year after enrolment and the cost was on average 1% of those allocated to IA. Children with a faecolith spent on average 2.6 times longer in hospital as those without, and cost of treating these children was on average 6.3 times that of those without a faecolith. Children allocated to receive AO spent on average 10% of the time in hospital that those allocated to IA during the first year after enrolment and the cost was on average 1% of those allocated to IA. Children with a faecolith spent on average 2.6 times longer in hospital as those without, and cost of treating these children was on average 6.3 times that of those without a faecolith.

Since not all children received their allocated intervention, a secondary analysis based on the treatment actually received was performed. Outcomes were compared for 45 children who underwent IA and 55 who received AO. Baseline characteristics between these groups were similar (Web Appendix page 2, Table A2). In the 45 children who actually received IA, 3 met the criteria for the primary outcome in that they developed a significant complication following IA, giving an incidence of 7% (95% CI 2, 19). In the AO group, 6/55 children developed histologically proven recurrent acute appendicitis within the 1 year follow-up period (incidence 11% [95% CI 5, 22]). A further 5 children underwent appendicectomy for acute or chronic abdominal pain. Therefore, a total of 11 children in the AO group underwent appendicectomy in the 1 year follow-up period (20% [95% CI 11, 33]).

In this analysis both total length of hospital stay and cost were significantly lower in the AO group compared to IA group in both univariate and multivariate analysis. As in the ITT analysis there was a statistically significant relationship between presence of a faecolith and cost of treatment. These data are shown in the Web Appendix page 2, Tables A3 and A4.

Finally we explored whether there was any difference in incidence of histologically proven recurrent appendicitis or appendicectomy within 1 year of enrolment in children allocated to AO (ITT) or receiving AO (PTR) depending on gender and presence of a faecolith. The incidence of both these outcomes was similar regardless of presence of faecolith and gender in both ITT (Web Appendix pages 3-4 Figures A1 and A2) and PTR analyses .

## DISCUSSION

This study was designed to generate high quality prospective data to inform the decision of whether interval appendicectomy is justified following successful non-operative treatment of an appendix mass in children. Data were acquired from a population of children who initially presented with an appendix mass, were successfully treated without appendicectomy (or any other appendix related procedure) and subsequently allocated to either 1 year of active observation or planned elective interval appendicectomy. The study design allows for truly comparative data to be obtained minimising the influence of bias that may exist if data were recorded from observational cohorts only. Treatment groups were well matched for age, gender and presence of a faecolith.

The main results of our study are that in children under active observation, 12% developed histologically proven recurrent appendicitis and 23% had an appendicectomy within 1 year of randomisation. The presence of a faecolith had no influence on the frequency of either of these outcomes. Although interval appendicectomy carries a low complication rate (6%), complications may be significant including need for return to the operating theatre in 2%. Overall, the cost of AO is less than IA.

Prior to embarking on this study we undertook a systematic review of the existing literature.<sup>7</sup> The volume of relevant literature was small, with just 3 articles reporting on rate of recurrent appendicitis in this specific patient population.<sup>8-10</sup> The overall weighted incidence of recurrence based on these previous data was 21%. In this prospective study we now report the incidence of recurrent appendicitis, as defined by histological examination of the appendix as 12%.

Appendicectomy is a frequently performed procedure in general paediatric surgical practise and all surgeons were experienced in the procedure at the start of the study. Although our study confirms previous reports that interval appendicectomy is generally a safe procedure with low morbidity, it is noteworthy that one child in this study suffered the significant complication of laparoscopic port-site hernia requiring subsequent bowel resection. Two further children developed wound infections requiring treatment with antibiotics. Clearly, avoiding interval appendicectomy would have avoided exposure to these complications but carries the risk of recurrence. Unexpectedly, two children developed recurrent appendicitis prior to their planned IA having previously had complete resolution of symptoms of appendix mass. Most surgeons will delay IA by a number of months in order to allow peritoneal inflammation to subside following the initial presentation. Our study demonstrates that recurrence during this interval is certainly possible.

Regarding missing an alternative diagnosis in children undergoing active observation, the most important in children is that of a carcinoid tumour of the appendix. No child in this study who underwent appendicectomy, whether planned or unplanned, was found to have a carcinoid tumour. Our previous systematic review estimated the risk of carcinoid tumour in this population as less than 1% which is similar to previous series of appendicectomies.<sup>12</sup> This figure is within the range of overall incidence in the general population of developing a carcinoid tumour at any site.<sup>13</sup>

In this study we have shown the cost of AO to be significantly less than that of IA. Although we did not undertake a full cost effectiveness analysis, we included the most significant healthcare associated costs related to each treatment approach, including both scheduled and unscheduled hospital attendances and admissions. We did not, however, include costs related to visits to the general practitioner or other healthcare related costs. We acknowledge that with decreasing admission times related to interval appendicectomy the cost of IA may be reduced further. In this study centres were free to use their standard practice including day case surgery if appropriate. In

our analysis, both duration of hospitalisation and time spent away from normal daily activities were significantly less for children in the AO arm as opposed to IA. We did not include the additional effect of this on parental activity, for example days absent from work. These results are similar to a previous study that investigated the cost of interval appendicectomy following perforated acute appendicitis.<sup>14</sup>

In addition to those children who had an appendicectomy during the 1 year follow-up period for histologically proven acute appendicitis, a further 5 children underwent appendicectomy for either acute or chronic abdominal pain. Histology of these appendices did not reveal acute inflammation. Thus a total of 11 children in the AO group underwent symptomatic appendicectomy. Despite this, over 75% of children under AO did not undergo appendicectomy within 1 year. This is likely to be a pragmatic statistic to use for the purposes of counselling parents.

We did not detect an increased incidence of recurrent appendicitis in children who had a faecolith. A previous report suggested that a faecolith may increase the risk of recurrence<sup>9</sup> and for this reason we specifically included it as one of the minimisation criteria. Of the 12 children with a faecolith allocated to AO, just 2 (17%) developed histologically proven recurrent appendicitis during the follow-up period and one additional child underwent appendicectomy for a second episode of acute right iliac fossa pain 6 months after enrolment; histology revealed lymphoid hyperplasia only with no inflammation, yielding an appendectomy rate of 25%. Interestingly, across both treatment groups, the cost of treating children with a faecolith was significantly higher than children without a faecolith. However, the additional cost associated with treating a child with a faecolith was less than the cost benefit of AO (compared to IA).

The strengths of this study are principally in its design. To our knowledge this is the first prospective study to report on outcomes of children with an appendix mass and is also the only randomised study designed to address this important clinical question. The study was carried out at multiple centres making it likely that our findings are generalisable to the target population. The principal limitation is that children in the AO group were followed up for only 1 year whilst the risk of recurrent appendicitis or need for subsequent appendicectomy is clearly lifelong. We intend to follow these children up in the future for a total of 5 years following initial enrolment. An additional limitation is that we were unable to blind participants or observers to the allocated treatment due to the nature of the interventions. However all outcomes were assessed using predefined, objective criteria. In addition, recruiting surgeons did not have access to patient allocation data, aggregated data, or data other than individual patient data in the course of usual clinical care.

In conclusion, this prospective randomised study has provided high quality data on which clinicians, parents and children can, for the first time, make an evidence-based decision regarding the justification for interval appendicectomy. In children who do not have routine interval appendicectomy the risk of recurrent histologically confirmed appendicitis is 12% in the first year and over 75% will have avoided appendicectomy one year later. Observation alone results in fewer days in hospital, fewer days away from normal daily activities and is cheaper than routine interval appendicectomy.

**Conflict of interest statements:**

None of the authors declare any conflict of interest, financial or otherwise in relation to this work

### **Authors contributions:**

Nigel Hall conceived and designed the study, was the study co-ordinator, helped perform data analysis, interpreted the data, wrote the draft of the manuscript and approved the final manuscript submitted.

Simon Eaton designed the study, provided data analysis for the TSC, performed the statistical analysis, created figures, interpreted the data, revised the manuscript and approved the final manuscript submitted.

Michael Stanton designed the study, recruited patients, collected data, revised the manuscript and approved the final manuscript submitted.

Agostino Pierro conceived and designed the study, recruited patients, collected data, revised the manuscript and approved the final manuscript submitted.

David Burge conceived and designed the study, recruited patients, assisted with data collection revised the manuscript and approved the final manuscript submitted.

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#### the CHINA study collaborators

Paolo de Coppi (Great Ormond Street Hospital, London, UK)

Ashwini Joshi (Royal London Hospital, London, UK)

Simon Clarke (Chelsea and Westminster Hospital, London, UK)

Sanja Besarovic (Hull Royal Infirmary, Kingston-upon-Hull, UK)

Thomas Tsang (Norfolk and Norwich University Hospital, Norwich, UK)

Ingo Jester, Girish Jawaheer (Birmingham Children's Hospital, Birmingham, UK)

Harriet Corbett (Alder Hey Childrens Hospital, Liverpool, UK)

Niyi Ade-Ajayi (King's College Hospital, London, UK)

Haitham Dagash, Shawqui Nour (Leicester Royal Infirmary, UK)

Merril McHoney (Royal Hospital for Sick Children, Edinburgh, UK)

Bruce Jaffray (Royal Victoria Infirmary, Newcastle, UK)

Emma Sidebotham (Leeds General Infirmary, Leeds, UK)

Hugh Grant (John Radcliffe Hospital, Oxford, UK)

Masih Kader, Ali Keshtgar, Dorothy Kufeji (Evelina Children's Hospital, London, UK)

Jan F Svensson, Tomas Wester, Markus Almström, (Karolinska Institutet, Stockholm, Sweden)

Varadarajan Kalidasan (Royal Alexandra Children's Hospital, Brighton, UK)

David Marshall, Irene Milliken (Royal Belfast Hospital for Sick Children, Belfast, UK)

Brian Davies (Queens Medical Centre, Nottingham, UK)

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James Hamill (Starship Hospital, Auckland, New Zealand)

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**Table 1: Baseline characteristics of treatment groups**

	<b>IA group (n=50)</b>	<b>AO group (n=52)</b>
Age (years, median [IQR])	9 [5-12]	8 [4-11]
Male gender (n [%])	25 [50%]	26 [50%]
Presence of faecolith on imaging at initial presentation with appendix mass (n [%])	11 [22%]	12 [23%]

Allocation to each treatment group within centre is shown in the Web Appendix, Table A1 page 1.

**Table 2: Comparison of total length of hospital stay in 1 year from enrolment and cost between treatment groups (ITT analysis)**

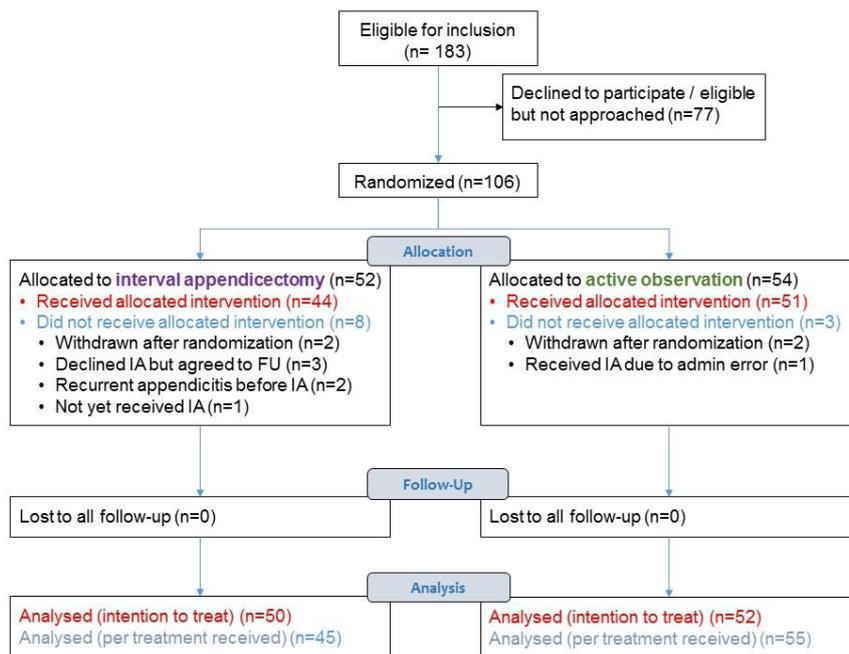
	<b>Allocated treatment group</b>		<b>p*</b>
	<b>Interval appendicectomy (n=50)</b>	<b>Active observation (n=52)</b>	
<b>Total length of stay (hours)</b>	32 (26-49)	0 (0-23)	p<0.0001
<b>Cost (UK £)</b>	1476 (1022-2211)	0 (0-444)	p<0.0001

Data are median (IQR); \*Mann-Whitney Test

**Table 3: Results of multiple linear regression analysis exploring relationship between treatment group and outcomes adjusting for minimisation factors (ITT analysis). Effect sizes are multiplicative compared with reference as regression analysis was performed on log-transformed data.**

	Adjusted effect size (95% CI)	P
<i>Total hospital stay in 1 year follow-up (hours)</i>		
<b>Gender</b>		
Female	reference	
Male	1.28 (0.67, 2.44)	0.46
<b>Presence of faecolith</b>		
No faecolith	reference	
Faecolith	2.65 (1.11, 6.30)	0.03
<b>Age</b>		
Age (per year older)	0.93 (0.84, 1.03)	0.18
<b>Treatment group</b>		
IA	reference	
AO	0.10 (0.06, 0.19)	<0.0005
<i>Cost in 1 year of follow-up (UK £)</i>		
<b>Gender</b>		
Female	reference	
Male	1.61 (0.50, 5.23)	0.42
<b>Presence of faecolith</b>		
No Faecolith	reference	
Faecolith	6.23 (1.30, 30.2)	0.02
<b>Age</b>		
Age (per year older)	0.85 (0.70, 1.02)	0.08
<b>Treatment group</b>		
IA	reference	
AO	0.01 (0.00, 0.02)	<0.0005

**Figure 1: Trial profile**



Active observation versus interval appendicectomy following successful non-operative treatment of appendix mass in children: a randomised controlled evaluation

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**Table A1: Centres, principal investigators and numbers recruited**

Centre	Principal investigator(s)*	Total number enrolled at site	Allocated to IA	Allocated to AO
Alder Hey Childrens Hospital, Liverpool, UK	Harriet Corbett	15	7	8
Birmingham Children's Hospital, UK	Ingo Jester, Girish Jawaheer	14	6	8
Southampton Children's Hospital, Southampton, UK	Michael Stanton	11	5	6
Evelina Children's Hospital, London, UK	Masih Kader, Alireza Keshtgar	9	5	4
Karolinska Institutet, Stockholm, Sweden	Jan F Svensson	9	5	4
Queens Medical Centre, Nottingham, UK	Brian Davies	7	4	3
Leeds General Infirmary, Leeds, UK	Emma Sidebotham	5	2	3
Royal Belfast Hospital for Sick Children, Belfast, UK	David Marshall, Irene Milliken	5	3	2
Royal Hospital for Sick Children, Edinburgh, UK	Merril McHoney	4	2	2
Chelsea and Westminster Hospital, London, UK	Simon Clarke	4	2	2
Norfolk and Norwich University Hospital, Norwich, UK	Thomas Tsang	4	2	2
Great Ormond Street Hospital, London, UK	Agostino Pierro, Paolo de Coppi	3	1	2
John Radcliffe Hospital, Oxford, UK	Hugh Grant	3	2	1
Starship Hospital, Auckland, New Zealand	James Hamill	3	1	2
Royal Victoria Infirmary, Newcastle, UK	Bruce Jaffray	3	2	1
King's College Hospital, London, UK	Niyi Ade-Ajayi	3	1	2
Royal Alexandra Children's Hospital, Brighton, UK	Kalidasan Varadarajan	2	1	1
Leicester Royal Infirmary, Leicester, UK)	Haitham Dagash, Shawqui Noor	1	1	0
Addenbrookes Hospital, Cambridge, UK	Stephen Farrell	1	0	1
Royal London Hospital, London, UK	Ashwini Joshi	0	0	0
Hull Royal Infirmary, Kingston-upon-Hull, UK	Sanja Besarovic	0	0	0

\* if more than one principal investigator listed then PI changed during study period

**Table A2: Baseline characteristics of treatment groups for comparison based on treatment actually received**

	<b>IA group (n=45)</b>	<b>AO group (n=55)</b>
<b>Demographics</b>		
Age (years, median [IQR])	9 [5-12]	8 [4-11]
Male gender (n[%])	21 [47%]	28 [51%]
Presence of faecolith on imaging at initial presentation with appendix mass (n [%])	11 [24%]	12 [22%]

**Table A3 Comparative outcomes between treatment groups based on treatment actually received**

<b>Comparative outcomes</b>			
Total length of stay (hours)	32 [27-48]	0 [0-17]	<0.0001 <sup>s</sup>
Cost (UK £)	1482 [1149-2138]	0 [0-400]	<0.0001 <sup>s</sup>

<sup>s</sup>Mann-Whitney test

**Table A4: Results of multiple linear regression analysis exploring relationship between treatment group and outcomes adjusting for minimisation factors (PTR analysis). Effect sizes are multiplicative compared with reference as regression analysis was performed on log-transformed data.**

	<b>Adjusted effect size (95%CI)</b>	<b>P</b>
<i>Total hospital stay in 1 year follow-up (hours)</i>		
<b>Gender</b>		
Female	reference	
Male	1.23 (0.67, 2.26)	0.49
<b>Presence of faecolith</b>		
No Faecolith	Reference	
Faecolith	2.28 (1.02, 5.09)	0.05
<b>Age</b>		
Age (per year older)	0.94 (0.86, 1.04)	0.23
<b>Treatment group</b>		
IA	reference	
AO	0.09 (0.05, 0.15)	<0.001
<i>Cost in 1 year of follow-up (UK £)</i>		
<b>Gender</b>		
Female	reference	
Male	1.65 (0.57, 4.72)	0.35
<b>Presence of faecolith</b>		
No faecolith	reference	
Faecolith	4.23 (1.04, 17.17)	0.04
<b>Age</b>		
Age (per year older)	0.87 (0.74, 1.04)	0.12
<b>Treatment group</b>		
IA	reference	
AO	0.00(0.00, 0.01)	<0.001

Figure A1: Incidence and timing of histologically proven recurrent appendicitis during 1 year follow-up (panel A) by presence of a faecolith (panel B) and gender (panel C) in children allocated to active observation (ITT analysis). Curves compared using log-rank test.

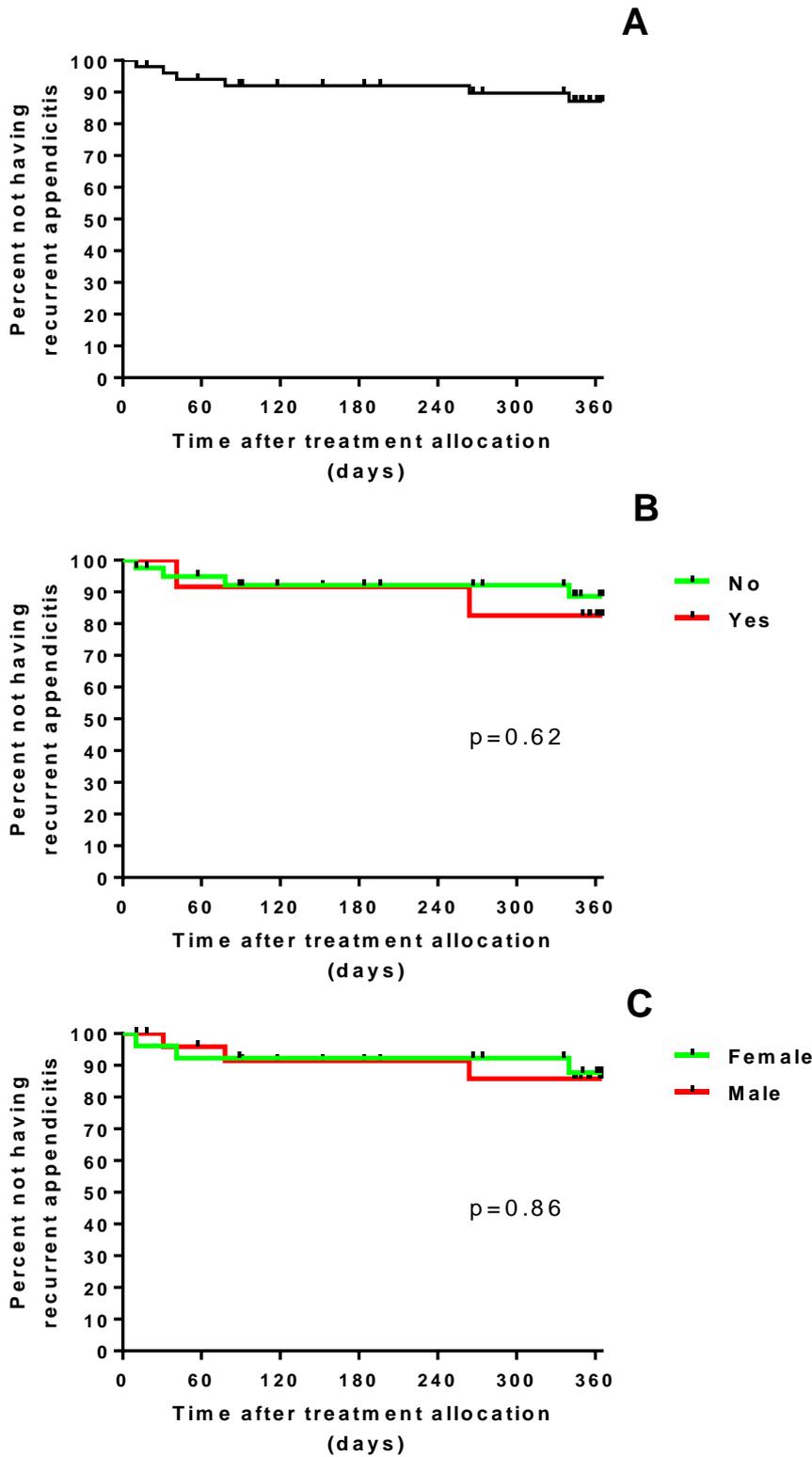


Figure A2: Incidence and timing of appendicectomy (any cause) during 1 year follow-up (panel A) by presence of a faecolith (panel B) and gender (panel C) in children allocated to active observation (ITT analysis). Curves compared by log-rank test

