A core outcome set for uncomplicated acute appendicitis research in children and young people

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Abstract

Introduction

Selection of outcomes that are important to patients as well as to health professionals is essential if studies are to inform policy and practice. Consistent selection of outcomes across studies aids comparison and combination of results. These can both be achieved by using core outcome sets. We aimed to develop a core outcome set for uncomplicated acute appendicitis in children and young people.

Methods

Systematic literature reviews, qualitative interviews with parents and patients treated for uncomplicated acute appendicitis, and a Study-Specific Advisory Group informed a long list of outcomes. Outcomes were then prioritised by stakeholders based in the United Kingdom (patients, parents, and paediatric and general surgeons) in an online three-round Delphi consensus process, followed by face-to-face consensus meetings.

Results

A long list of 40 items was scored by 147 key stakeholders in the first Delphi round, of whom 90 completed the two subsequent Delphi rounds. The final core outcome set comprises 14 outcomes: intra-abdominal abscess, re-operation (including interventional radiology procedure), readmission, bowel obstruction, wound infection, other wound complication, antibiotic failure, negative appendicectomy, recurrent appendicitis, death, patient stress/psychological distress, length of hospital stay, time away from full activities and quality of life.

Discussion

We used established consensus methods to develop a core outcome set for uncomplicated acute appendicitis in children. The core outcome set should be adopted by researchers to report outcomes of uncomplicated acute appendicitis in children in order to enhance the quality of research and facilitate comparison between trials. Further work will determine how and when to measure these outcomes.

INTRODUCTION

Acute appendicitis is the most common surgical emergency in children and young people[1], and although most surgeons consider appendicectomy to be the gold standard treatment, recent research has examined the use of non-operative treatment with antibiotics.[2] A systematic review of outcomes reported in randomised controlled trials and meta-analyses of acute appendicitis in children revealed wide heterogeneity in outcome selection.[3] Such differences make it challenging, sometimes impossible, to synthesise study results and conduct meta-analyses. Standardising outcomes by developing and implementing a 'core outcome set' facilitates data synthesis and ensures that outcomes of importance to relevant stakeholders are included. This study aimed to develop a core outcome set for future research of operative and non-operative treatments for uncomplicated acute appendicitis in children and young people (< 18 years).

METHODS

The study adopted established consensus methods,[4] involving three phases: phase 1, development of a long list of outcomes using systematic reviews and qualitative interviews with patients and parents; phase 2, a three-round online Delphi survey with key stakeholders (patients, parents, and paediatric and general surgeons) and; phase 3, two consensus meetings. The recommended core outcome set development standards were met when planning, conducting and reporting the project.[5, 6] The study was part of the CONservative TReatment of Appendicitis in Children - a randomised controlled Trial (Feasibility) - CONTRACT study (https://www.fundingawards.nihr.ac.uk/award/14/192/90), which received ethical approval (16/SC/0596).

A Study-Specific Advisory Group (SSAG) comprising children, young people and parents, that was assembled for the CONTRACT Feasibility Study[7] informed the development of study materials and a participant video (https://www.youtube.com/watch?v=JeSZf2jmWCc). Some members also attended the patient and parent consensus meeting to facilitate discussion. The study protocol has been published elsewhere[8] and was registered with the COMET Initiative in May 2017 (http://www.comet-initiative.org/studies/details/987).

Scope of the core outcome set

The core outcome set is intended for use in future research (including clinical trials) that evaluates the overall success of operative or non-operative treatment (i.e. antibiotics) in children and young people <18 years, with uncomplicated acute appendicitis.

Phase 1: developing a long list of outcomes

A long list of outcomes was developed from two sources; firstly from recent systematic literature reviews to identify previously reported outcomes in trials examining the treatment of uncomplicated acute appendicitis in children and young people[2, 3], and secondly, from the CONTRACT Communication Study embedded within the CONTRACT Feasibility trial. This involved semi-structured qualitative interviews with patients and

parents who participated in the CONTRACT Feasibility Study[7] to explore which outcomes were important to them. Researchers (FS, SE and NH) subsequently mapped outcomes identified from the qualitative study to outcomes identified from the literature reviews to determine whether there were any additional outcomes. This long list was then refined to avoid duplication. The SSAG were presented with draft text, including outcome names and descriptions, and instructions on outcome scoring, for the Delphi survey website. The group were asked to annotate and discuss the text and design on the Delphi website to improve clarity and comprehensibility. Additional outcomes suggested by the SSAG were also considered for inclusion. The group's feedback was used to revise the Delphi website before invitations were sent to potential participants.

Phase 2: three-round online Delphi surveys

A three-round online Delphi survey was used to develop the core outcome set.

Stakeholder identification

Stakeholders were separated into three panels: (i) patients; (ii) parents; (iii) paediatric or general surgeons who treat children with appendicitis. Patients (aged 12-18 years) and parents of patients (aged 5-18 years), who had either received treatment or whose children had received treatment for uncomplicated acute appendicitis in the preceding 24 months, were invited to participate at seven specialist children's hospitals, across five geographical regions in England.

Paediatric surgeons in the UK who treat children with uncomplicated acute appendicitis were invited to participate via the membership list of the British Association of Paediatric Surgeons (including consultants and trainees), and through professional contacts of the investigators. General surgeons who regularly treat children with uncomplicated acute appendicitis were invited to participate via the Association of Surgeons of Great Britain and Ireland, existing professional contacts and regional surgical networks within the UK.

Stakeholders from outside the UK were not invited as this would have posed logistical and resource challenges given that the intention was to include patients, parents and surgeons.[4]

Stakeholder registration

Stakeholders received an invitation letter and information sheet with a link to a study website, allowing them to access further information, view the study video and register. Registration was open for approximately 10 weeks until the desired number of stakeholders registered d (minimum of 10 per panel). We aimed for 75-100 stakeholders in the Delphi first round with equal numbers in each stakeholder panel.[9]

Delphi surveys

An online three-round Delphi survey was conducted in parallel across all stakeholder panels. Software developed by the National Perinatal Epidemiology Unit [University of Oxford, UK], which had previously been used successfully to develop two paediatric surgical core outcome sets,[10, 11] was hosted on a secure server..

Stakeholders were presented with the long list of outcomes arranged into themes. In all three Delphi rounds, stakeholders were asked to score each outcome using the Grading of Recommendations, Assessment Development and Evaluations (GRADE) scale, which is commonly used in the development of core outcome sets. The scale allows stakeholders to score the importance of each outcome from 1 to 9, with 1 to 3 labelled 'not important', 4 to 6 labelled 'important but not critical' and 7 to 9 labelled 'critical' for inclusion in a core outcome set.[12] Stakeholders could propose other outcomes at the end of the round one survey. These were reviewed and mapped to the existing long list if appropriate. New outcomes were added to the long list in round two if: (1) the study team were not in agreement that the outcome could be mapped to one on the existing long list; (2) they were defined as an outcome,[4] and; (3) were proposed by at least two stakeholders.

All stakeholders who completed each round were invited to participate in the subsequent round. In round two, participants were provided with feedback from their own stakeholder panel and in round three from all stakeholder panels, in order to build consensus between stakeholder panels and then across panels.[11]

Scores for each outcome were analysed for each stakeholder panel and descriptive statistics generated at the end of each round. As per the GRADE scoring system, the consensus status of each outcome was defined at the end of each round. 'Consensus in' was defined as ≥ 70% of stakeholders rating the outcome 7–9, and < 15% rating it as 1–3. 'Consensus out' was defined as > 70% stakeholders rating it 1–3 and < 15% rating it 7–9. 'No consensus' was defined as outcomes that met neither 'consensus in' nor 'consensus out'.

In round two, all stakeholders were asked to rescore each outcome, taking into account how others in their stakeholder panel had scored the outcome. Stakeholders were also asked to score any new outcomes.

In round three attrition was noted among the patient panel. Since the aim was to ensure the final core outcome set represented the views of children and young people, in addition to parents and surgeons, all patients who completed round one were invited to participate in round three. All stakeholders were again asked to rescore each outcome taking into account how others in their panel and stakeholders in the other two panels had scored the outcome in round two.

Phase 3: consensus meetings

The study team emailed surgeons and parents who completed all three rounds of the Delphi survey, together with all patients who had registered for the study (to increase patient representation), to invite them to attend a consensus meeting in Birmingham, UK in June 2018. However, far fewer stakeholders were able to attend than anticipated, so the study team agreed to postpone the consensus meeting. Following consultation with stakeholders, the study team held two separate consensus meetings. Although this deviated from the study protocol, other core outcome set developers have used this approach and suggest that holding separate meetings for patients and health professionals may help avoid the risk that meetings are dominated by health professionals.[13] The surgeons' meeting was held in September 2018 in London and the parents' and patients' meeting was held in September

2018 in Birmingham. Travel expenses, accommodation and childcare were provided. A £75 voucher was offered to parents and patients for participating, informed by guidance on patient and public involvement in research.[14]

All attendees were sent a consensus meeting booklet describing the study aims, purpose of the consensus meetings, and an overview of the Delphi results. A chairperson was selected for each meeting with expertise in core outcome set development to promote and potentially mediate discussion. EW (Patient and Public Involvement Lead on the CONTRACT Feasibility Study) and two families from the SSAG also attended the parents' and patients' consensus meeting to help facilitate discussion, but did not vote. The meetings included an overview of the study so far, instructions for the meeting, discussion of outcomes and anonymous voting using TurningPoint electronic software (Turning Technologies, Youngstown, Ohio, USA).

Due to attrition (particularly among patients) and potential response bias, the study team prioritised which outcomes to discuss and rescore in the meetings, rather than rescoring all outcomes as previously proposed.[8] For outcomes where ≥70% of stakeholders across all panels rated the outcome 7–9, brief discussion took place. Following discussion, the chair asked stakeholders whether they felt that any of those outcomes should be excluded from the final core outcome set and outcomes were only rescored if stakeholders voiced a preference to revote. For outcomes where <50% of stakeholders across all stakeholder panels rated the outcome 7-9 at the end of the third Delphi round, again, brief discussion took place, with an option to rescore if stakeholders voiced a preference to revote. All other outcomes (i.e. those 50-70%) were presented, discussed, and rescored, unless stakeholders felt strongly that following discussion rescoring was unnecessary. Following discussion and rescoring, outcomes reaching 'consensus in' at either meeting were included in the final core outcome set in line with previous similar designs.[13, 15]. All other outcomes were excluded.

Data analysis

Descriptive statistics were used to calculate the scores for each outcome, which were analysed in total and for each stakeholder panel, at each round. The data analysis process from round one was repeated for rounds two and three. The study team included partial respondents in the analysis and examined whether attrition had an effect on outcome scores graphically, as recommended in the COMET Handbook[4] and using a multilevel modelling approach (level one: outcome; level two: participant; level three: stakeholder panel) using MLwiN Version 3.01 (Centre for Multilevel Modelling, University of Bristol, UK).

RESULTS

Phase one: developing a long list of outcomes

The qualitative team identified eight outcomes of importance to families but all of these mapped to outcomes already identified from the reviews (Supplementary File 1). Thus no new outcomes were revealed and a long list of forty outcomes was generated (Supplementary File 2) categorised into themes: (1) Outcomes during an operation (if performed); (2) Outcomes that may occur after treatment; (3) Duration of recovery; (4) Additional (unplanned) procedures

during the first hospital admission; (5) Outcomes related to pain; (6) Other complications; (7) Outcomes reported by patients; (8) Cost of treatment and resources used; (9) Other outcomes.

Phase two: three-round online Delphi surveys

Between October and December 2017, 818 parents and patients from seven NHS sites in England were invited to participate in the study**.** It was not possible to precisely measure the number of paediatric and general surgeons who were invited to participate.

Overall, 195 stakeholders registered, (15 patients, 67 parents, 57 paediatric surgeons, and 56 general surgeons, Figure 1). The median ages for patients who registered, completed rounds one, two, and three were 12.5 (range=11-18), 13.5 (range=11-18), 12 (range=12-14), and 14 years, respectively. The median age for patients of parents who registered, completed rounds one, two, and three was 10 (range=3-18) years throughout.

Twenty-six stakeholders in round one proposed 35 additional outcomes (Supplementary File 3), of which three outcomes were agreed to be new and included in subsequent rounds: 'Psychological distress'; 'Negative appendicectomy', and 'Time to normal diet'.

None of the outcomes were voted 'consensus out' in any round of the Delphi. Table 1 summarises outcome scores across each Delphi round and Supplementary File 4 shows outcome scores for each stakeholder panel, by Delphi round. Attrition analysis indicated no systematic significant difference in responders and non-responders between round one and round two, and round one and round three. On average, round one scores were 6.1±0.2 for those that completed round one only, and were increased by 0.1±0.2 in those that also completed round two [p=0.61], round one scores were increased by 0.1±0.3 in those that also completed round three [p=0.60]. Median scores of individual items, and score frequency distributions were also similar between responders and non-responders (see Supplementary File 5).

Phase three: consensus meetings

Overall, 28 stakeholders participated in the consensus meetings (see Figure 1).

Surgeon consensus meeting

Ten paediatric surgeons and 7 general surgeons attended. During the meeting, several outcomes warranted extended discussion and/or a second vote. Some were outcomes that were not voted 'consensus in' in round three of the Delphi but which surgeons strongly felt were important to include in the core outcome set - 'Negative appendicectomy', 'Time away from full activity', 'Length of hospital stay' and 'Wound infection'. Following discussion and voting surgeons reached consensus to include these outcomes.

Other outcomes that were discussed had reached 'consensus in' in the Delphi survey but surgeons did not reach consensus to include these outcomes at the meeting. 'Unplanned central venous catheter' was felt to be a complication (rather than an outcome), rare in the context of uncomplicated appendicitis and a measure of practice rather than treatment success. 'Blood loss' was felt not specific enough and surgeons proposed that it was not important unless a transfusion was required. The outcome was redefined to 'Blood loss requiring transfusion' and a subsequent vote held but still did not achieve 'consensus in'.

Surgeons also felt that 'Major or minor complications' was too vague and could include too many things for it to be meaningfully included in a core outcome set.

Two other outcomes were discussed by surgeons. It was proposed and agreed that 'Interventional radiology procedure' should be combined with another outcome that achieved 'consensus in' - 'Re-operation' since in a child they would both be procedures under general anaesthesia. 'Other infectious complication' was discussed further with reference to the implications that this complication could have. Surgeons felt an infectious complication would be deemed as critically important if it resulted in re-operation but less important if it did not. They therefore agreed that 'Other infectious complication' should not be included in the core outcome set, because 'Re-operation' had already achieved 'consensus in'.

In total, surgeons agreed to include 12 outcomes in the core outcome set: 'Intra-abdominal abscess', 'Re-operation' (including 'Interventional radiology procedure'), 'Bowel obstruction', 'Readmission to hospital', 'Death', 'Quality of life', 'Recurrent appendicitis', 'Antibiotic failure' (in studies examining non-operative treatment), 'Wound infection', 'Length of hospital stay', 'Negative appendicectomy', and 'Time away from full activity'.

Patient and parent consensus meeting

In addition to the seven parents and one patient who had completed the third round of the Delphi survey, three further stakeholders attended. One was a patient (identified via a parent) who matched the study eligibility criteria but had not completed any of the previous Delphi surveys. The other two were parents who wished to accompany their respective partners to the meeting. These additional stakeholders reported completing the Delphi surveys alongside their partner. The study team discussed these cases and agreed that the additional patient and two parents could attend the meeting to increase patient and parent representation in the core outcome set development.

Again, during the meeting, several outcomes warranted extended discussion and/or a second vote. In round three of the Delphi survey, patients and parents were not in consensus to include 'Psychological distress' and parents were not in consensus to include 'Negative appendicectomy' but in the meeting, patients and parents reached consensus to include both outcomes. 'Patient stress' achieved 'consensus in' and with one additional vote 'psychological distress' would have also achieved 'consensus in'. Following discussion it was agreed to include 'patient stress / psychological distress' as a combined outcome in the final core outcome set.

In Delphi round three, patients and parents were in consensus to include 'Major or minor complications', 'Pain score', and 'Fever after treatment', and parents were in consensus to include 'Blood loss'. However, patients and parents did not reach consensus to include any of these outcomes following discussion at the meeting. 'Pain score', and 'Fever after treatment' were not felt to be critically important and participants agreed that the importance of 'Blood loss' would depend on the amount and the effect of blood loss. Parents and patients suggested that the important aspect of 'Major or minor complications' was the need to capture a 'major' complication but that a 'minor' complication was less important. Since key major complications, such as 'Intra-abdominal abscess' and 'Bowel obstruction' were already included there was agreement not to include 'Major or minor complications'.

In total, parents and patients agreed to include 12 outcomes in the core outcome set: 'Intra-abdominal abscess', 'Re-operation' (including 'Interventional radiology procedure'), 'Bowel obstruction', 'Readmission to hospital', 'Death', 'Quality of life', 'Recurrent appendicitis', 'Antibiotic failure' (although it was suggested to only include this in studies examining non-operative treatment), 'Wound infection', 'Wound complication', 'Negative appendicectomy', and 'Patient stress / psychological distress'.

Finalising the core outcome set

Combining the surgeon and patient and parent outcome sets resulted in a final core outcome set of 14 outcomes, including 'antibiotic failure' which need only be measured and reported in studies of non-operative treatment (Figure 1). The outcomes were aligned with OMERACT Filter 2.0 [16] domains (Figure 2).

Discussion

Previous work has demonstrated that the outcomes reported in research on uncomplicated acute appendicitis in children and young people vary widely.[2, 3] To optimise the relevance of future research in this field and to facilitate comparison of outcomes between studies, we developed a core outcome set using established methodology.[4] The final core outcome set includes 14 outcomes. Development of a core outcome set for this condition is particularly timely as there is currently great interest in non-operative management of uncomplicated acute appendicitis in children and young people.[17, 18] Further work is necessary, following the COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) to define and measure the core outcomes[19], for example selection of the appropriate measure for 'child's quality of life'.

One of the strengths of our study was the inclusion of children and young people and parent stakeholders to ensure that important outcomes were considered and included that might otherwise be overlooked.[20] Although adult patients have been increasingly included in the development of core outcome sets,[4] few core outcome sets have included both children and parents as stakeholders. Of those studies that have, the degree to which children and parents have been able to contribute their views on which outcomes are important at all stages of the consensus process has varied.[21, 22] Engaging these important stakeholders in the development of this core outcome set and maintaining their engagement was challenging. To an extent, the study team anticipated this and young people and parents from our SSAG were consulted in advance to inform study materials and adjust methods to optimise engagement. Despite this, the proportion of young people and parents who registered and engaged in all stages of the study was lower than anticipated. In discussing this with families, they indicated that having recovered from appendicitis, patients and parents had moved on with their lives such that appendicitis was often something that had been 'forgotten'. Furthermore, as uncomplicated appendicitis is an acute condition and the extent of involvement of health professionals from various disciplines is arguably more limited than for chronic conditions, the study team did not include an expansive range of health professional stakeholder panels. The focus was primarily on those likely to be most affected (young people and parents) and those who typically determine treatment decisions (surgeons). Previous studies have adopted a similar approach,[23-25] but it is acknowledged

that methods may have been strengthened by including a broader range of health professional stakeholder roles.

A potential limitation of this study is that it was conducted within the UK only. While this strengthens the validity of the core outcome set for future UK-based research studies, international ratification or validation of the core outcome set should take place before adoption in other countries. Researchers planning to use this core outcome set in other geographical areas should determine its applicability to their research setting by using critical appraisal tools, such as COS-STAD.[6] Recently a protocol for an international core outcome set for treatment of uncomplicated appendicitis in children has been published.[26]

Having developed a core outcome set for studies in uncomplicated acute appendicitis in children and young people using robust consensus methods, the surgical community should now adopt the core outcome set for future studies. Such adoption will optimise the quality of research in this field and ensure that the outcomes measured are clinically relevant to patients, parents and surgeons. Future work is needed to agree how best the core outcomes should be measured.

Collaborators

The following members of The Appendicitis Core Outcome Set Study Group are collaborators on this study: Dean Rex, Kamila Kalka (St George's Hospital, London), Sean Marven, Joshua Rae (Sheffield Children's Hospital), Siminas Sotirios, Sarah Braungart (Royal Manchester Children's Hospital), Oliver Gee, Clare Skerritt (Birmingham Children's Hospital), Bhanu Lakshminarayanan, Rebecca Lisseter (Leeds General Infirmary), Rachel Brampton, Lisa Luedekke (Southampton Children's Hospital), and Harriet Corbett (Alder Hey Hospital, Liverpool).

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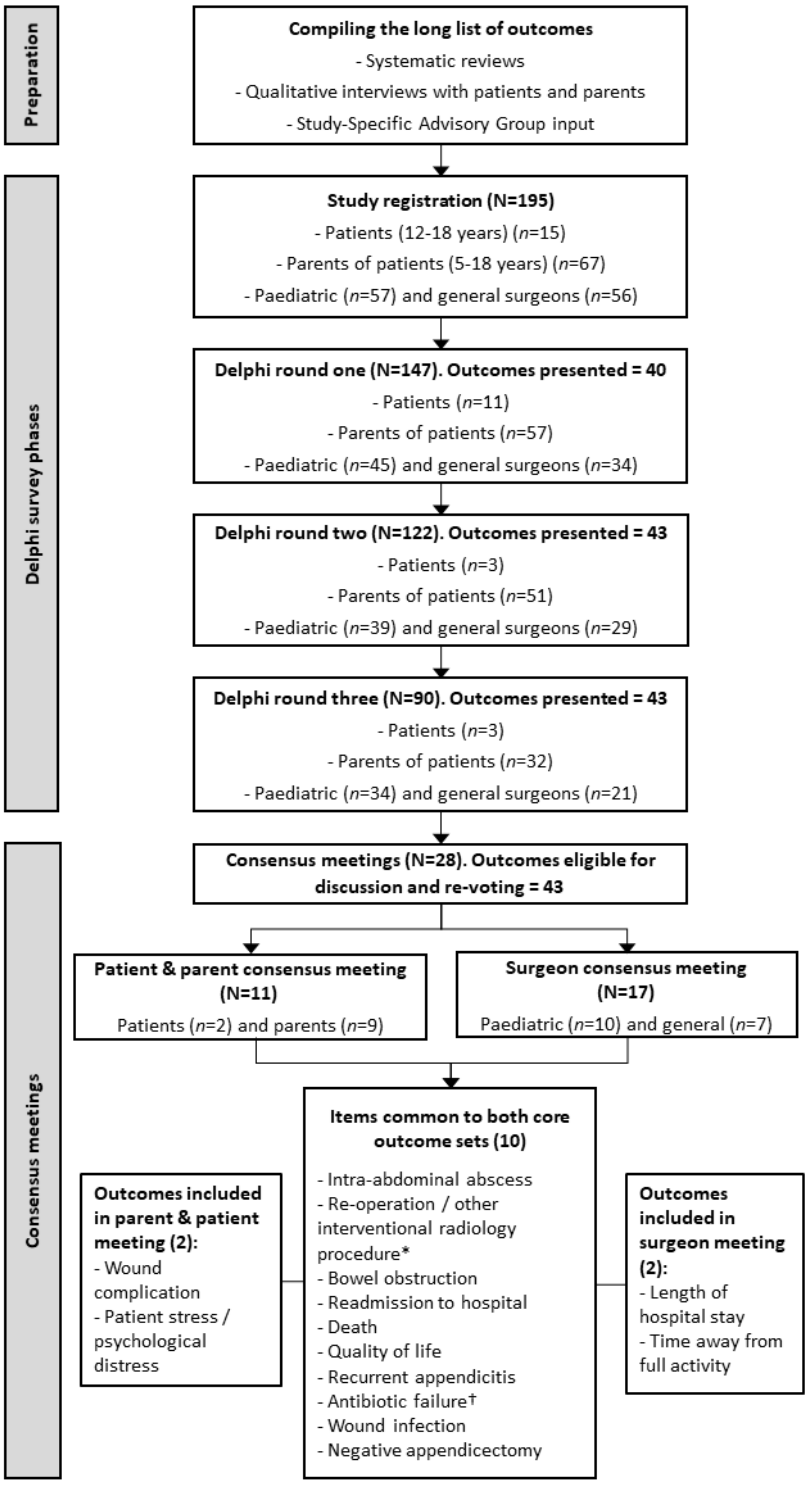
Table 1. Summary of stakeholder outcome ratings across Delphi rounds and final consensus on outcomes at consensus meetings.

Outcome	DELPHI ROUNDS Stakeholders who voted outcome 'very important' (score of 7-9) (*n*, %)			CONSENSUS MEETINGS Final core outcome set decision (Included/excluded)	
	Round 1 (*n*=147)	Round 2 (*n*=122)	Round 3 (*n*=90)	Surgeon meeting (*n*=17)	Parent and patient meeting (*n*=11)
Operation time	49 (34%)**	39 (32%)**	24 (26%)**	Excluded	Excluded
Conversion to open operation	56 (41%)**	57 (47%)**	35 (39%)**	Excluded	Excluded
Blood Loss	87 (63%)**	96 (79%)*	70 (77%)*	Excluded	Excluded
Wound infection	90 (61%)**	78 (63%)**	60 (65%)**	Included	Included
Intra-abdominal abscess	126 (85%)*	118 (97%)*	87 (96%)*	Included	Included
Wound complication	93 (64%)**	79 (64%)**	59 (64%)**	Excluded	Included
Fever after treatment	70 (47%)**	59 (48%)**	37 (41%)**	Excluded	Excluded
Blood markers of inflammation	58 (42%)**	54 (45%)**	30 (33%)**	Excluded	Excluded
Other infectious complication	60 (43%)**	54 (45%)**	30 (33%)**	Excluded	Excluded
Duration of antibiotics	47 (33%)**	36 (30%)**	14 (15%)**	Excluded	Excluded
Recovery of bowel function	51 (35%)**	43 (35%)**	23 (25%)**	Excluded	Excluded
Time to ambulation	60 (42%)**	50 (41%)**	27 (29%)**	Excluded	Excluded
Length of hospital stay	70 (47%)**	56 (46%)**	50 (54%)**	Included	Excluded
Duration of drainage	50 (41%)**	55 (49%)**	40 (47%)**	Excluded	Excluded
Unplanned CT scan	41 (31%)**	36 (30%)**	27 (31%)**	Excluded	Excluded
Any unplanned imaging	33 (25%)**	26 (22%)**	15 (17%)**	Excluded	Excluded
Interventional radiology procedure	54 (45%)**	76 (66%)**	62 (71%)*	Excluded†	Excluded
Unplanned Central Venous Catheter	56 (46%)**	76 (65%)**	67 (75%)*	Excluded	Excluded
Re-operation	98 (75%)*	112 (93%)*	84 (94%)*	Included	Included
Antibiotic failure	80 (59%)**	84 (71%)*	68 (77%)*	Included	Included
Analgesia	45 (31%)**	43 (35%)**	26 (29%)**	Excluded	Excluded
Pain score	66 (45%)**	59 (48%)**	47 (52%)**	Excluded	Excluded

Readmission to hospital	102 (71%)*	104 (86%)*	77 (88%)*	Included	Included
Bowel obstruction	121 (86%)*	114 (94%)*	84 (94%)*	Included	Included
Recurrent appendicitis	112 (81%)*	108 (90%)*	82 (92%)*	Included	Included
Major or minor complication	95 (68%)**	103 (85%)*	81 (91%)*	Excluded	Excluded
Death	125 (88%)*	115 (95%)*	84 (96%)*	Included	Included
Time away from school	62 (43%)**	56 (46%)**	39 (44%)**	Excluded	Excluded
Time away from full activity	40 (28%)**	29 (24%)**	16 (18%)**	Included	Excluded
Parent time off work	34 (24%)**	33 (27%)**	17 (19%)**	Excluded	Excluded
Wound healing time	41 (29%)**	37 (31%)**	24 (27%)**	Excluded	Excluded
Child's quality of life	96 (66%)**	103 (85%)*	85 (94%)*	Included	Included
Cosmesis	32 (25%)**	31 (27%)**	23 (26%)**	Excluded	Excluded
Parental stress	41 (28%)**	34 (28%)**	18 (21%)**	Excluded	Excluded
Patient stress	76 (52%)**	74 (61%)**	59 (66%)**	Excluded	Included †
Total cost of treatment	38 (28%)**	28 (23%)**	14 (16%)**	Excluded	Excluded
Cost effectiveness	57 (42%)**	50 (41%)**	36 (41%)**	Excluded	Excluded
Total healthcare visits	37 (27%)**	30 (25%)**	17 (19%)**	Excluded	Excluded
Duration of home healthcare	25 (19%)**	11 (9%)**	5 (6%)**	Excluded	Excluded
Bacterial peritoneal cultures	36 (29%)**	33 (29%)**	24 (28%)**	Excluded	Excluded
Psychological distress	‡	53 (44%)**	38 (43%)**	Excluded	Included †
Negative appendicectomy	‡	42 (38%)**	30 (35%)**	Included	Included
Time to normal diet	‡	25 (21%)**	13 (15%)**	Excluded	Excluded

*Consensus in; **No consensus; ***Consensus out; †Item combined with another item in the final core outcome set; ‡Outcomes introduced in round two; It is only necessary to report antibiotic failure in studies of non-operative treatment.

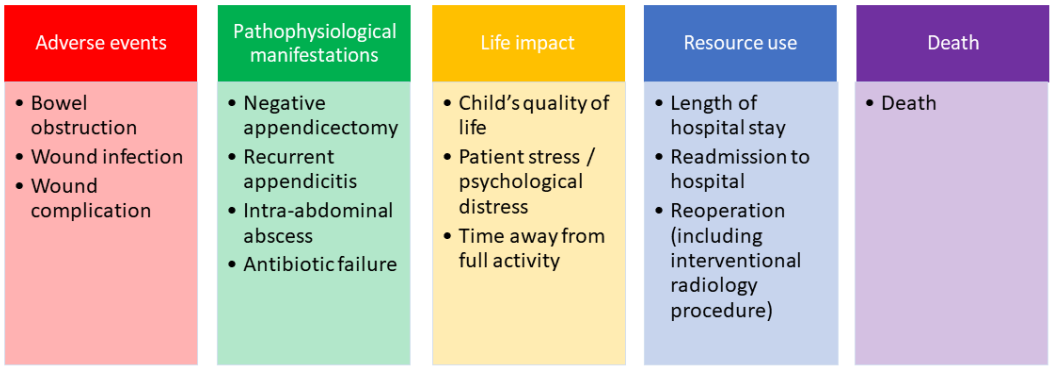
Figure 1


Preparation
Compiling the long list of outcomes
- Systematic reviews
- Qualitative interviews with patients and parents
- Study-Specific Advisory Group input
Delphi survey phases
Study registration (N=195)
- Patients (12-18 years) (n=15)
- Parents of patients (5-18 years) (n=67)
- Paediatric (n=57) and general surgeons (n=56)
Delphi round one (N=147). Outcomes presented = 40
- Patients (n=11)
- Parents of patients (n=57)
- Paediatric (n=45) and general surgeons (n=34)
Delphi round two (N=122). Outcomes presented = 43
- Patients (n=3)
- Parents of patients (n=51)
- Paediatric (n=39) and general surgeons (n=29)
Delphi round three (N=90). Outcomes presented = 43
- Patients (n=3)
- Parents of patients (n=32)
- Paediatric (n=34) and general surgeons (n=21)
Consensus meetings
Consensus meetings (N=28). Outcomes eligible for discussion and re-voting = 43
Patient & parent consensus meeting (N=11)
Patients (n=2) and parents (n=9)
Surgeon consensus meeting (N=17)
Paediatric (n=10) and general (n=7)
Items common to both core outcome sets (10)
- Intra-abdominal abscess
- Re-operation / other interventional radiology procedure*
- Bowel obstruction
- Readmission to hospital
- Death
- Quality of life
- Recurrent appendicitis
- Antibiotic failure†
- Wound infection
- Negative appendicectomy
Outcomes included in parent & patient meeting (2):
- Wound complication
- Patient stress / psychological distress
Outcomes included in surgeon meeting (2):
- Length of hospital stay
- Time away from full activity
*Reoperation was redefined to include interventional radiology procedure
†Antibiotic failure needs only to be reported in studies of non-operative treatment

1

2 Figure 2

Figure 2. Final core outcomes, grouped by OMERACT domains.



3

Supplementary File 1. Mapping of outcomes generated from the qualitative interviews with patients and parents to outcomes generated from the systematic reviews

Outcome from qualitative work	**Mapped outcome from systematic reviews**
Pain	Pain score or analgesia
Loss of appetite	Recovery of bowel function
Readmission to hospital	Readmission to hospital
Wound healing	Wound infection, wound healing time, or wound complication.
Child's psychological wellbeing	Child's quality of life
Time away from school	Time away from school
Time away from physical activity	Time away from full activity
Post-treatment fever	Post-treatment fever

Supplementary File 2. Long list of outcomes and descriptions presented in round one of the Delphi survey (Explanation is given where the outcome is different from the original 37 mapped outcomes).

Outcome	**Description**
Intra-abdominal abscess	A pocket of infected fluid or pus deep inside the tummy that may occur after appendicectomy of treatment with antibiotics and may require another procedure or more treatment with antibiotics.
Re-operation *(wording changed from ' Need for operation/re-operation)*	Having another operation that was not planned.
Bowel obstruction *(wording changed from 'Adhesive obstruction')*	A blockage of the intestine that would require treatment in hospital on may require an operation to treat it.
Major or minor complication	Any type of complication classified as a minor or major (excluding readmission to hospital, bowel obstruction and recurrent appendicitis).
Readmission to hospital	Needing to be readmitted to hospital with a stay at least one night.
Total healthcare visits *(wording changed from 'Healthcare visits')*	How many times the child visits a healthcare professional after they go home following their initial hospital treatment.
Any unplanned imaging *(wording changed from 'Post-treatment imaging')*	Having any type of x-ray or ultrasound test (other than CT scan) after treatment.
Total cost of treatment *(wording changed from 'Total charges')*	The total cost of treatment for the health service.

Duration of antibiotics	How long a child is treated with antibiotics for.
Duration of home healthcare	How long additional healthcare is needed at home after the child's initial hospital treatment.
Death	Dying (please bear in mind that the risk of dying from appendicitis is very low, but it may still be important to measure this as an outcome in studies).
Quality of life *(wording changed from 'Paediatric quality of life')*	The child's quality of life that is measured using a specifically designed questionnaire.
Recurrent appendicitis	Getting appendicitis again.
Antibiotic failure *(wording simplified from 'Complication of antibiotics or treatment intervention' as other complications can be included in 'major/minor complications')*	Operation to remove the appendix, due to antibiotic failure.
Blood Loss *(from additional 9 unmapped outcomes)*	Blood loss during the operation – losing lots of blood during an operation is unusual but you might think it is important to measure this.
Unplanned central venous catheter *(from additional 9 unmapped outcomes)*	Having a central venous catheter or not. A catheter is a fine tube inserted into a large vein to give medicines and usually used when medicines in to a vein are likely to be needed for over a week.
Wound infection	An infection at the site of the operation that requires treatment with antibiotics.

Wound complication (*wording changed from 'non-infectious wound complication')*	A complication with the surgical wound, such as the wound opening up before healing, or bleeding. This may need treatment with medicine or another procedure.
Interventional radiology procedure	Whether a child needs an interventional radiology procedure or not. Ain interventional radiology procedure is where an x-ray doctor puts a tube inside the tummy to drain pus, using an x-ray for guidance.
Patient stress *(proposed by Study-Specific Advisory Group)*	A measure of stress in the child that would be measured using a specifically designed questionnaire.
Hospital length of stay	How long a child has to spend in hospital.
Pain score	How severe a child reports that pain is, using a pain score.
Fever after treatment	A high temperature after treatment has started.
Duration of drainage	If a small tube (called a drain) is used after an operation or to drain pus from the tummy, the length of time this is needed for. This is unusual after treatment of uncomplicated appendicitis but can sometimes be needed.
Time away from school	How long a child has to spend away from school or their normal activities.
Other infectious complication	Other infection during or after treatment that is not related to the appendix or surgical wound. For example, a urine infection or chest infection.
Blood markers of inflammation	Results of blood tests that indicate how well the child is responding to treatment.
Analgesia (pain relief)	Number of doses and types of painkiller medicine (analgesia) that are needed.
Bacterial peritoneal cultures	Which bacteria are grown from inside a patient's tummy when fluid is tested.

Wound healing time *(from additional 9 unmapped outcomes)*	How long the wound takes to heal after an operation.
Cosmesis	Cosmesis is the neatness of a wound and whether the child or parent is happy with how it looks.
Time away from full activity	How long a child spends away from full activity, such as sport.
Cost effectiveness	Cost effectiveness involved working out how much a treatment costs, while also considering whether the treatment worked or not.
Conversion to open operation	If an operation that started out as keyhole (a few small holes) needs to be converted to an open operation (a larger cut).
Unplanned CT scan *(from additional 9 unmapped outcomes, Study-Specific Advisory Group suggested it was distinct enough from 'Any unplanned imaging' to be a separate outcome)*	Whether a CT (CAT) scan is needed after treatment or not. A CT scan makes more detailed pictures of parts of your body than an x-ray but uses higher dose of x-rays.
Time to ambulation (or get out of bed)	How long before the child can walk around or move normally.
Operation time	Time taken for the operation including time that the child is asleep for (under general anaesthetic).
Recovery of bowel function	How long it takes to be able to eat or pass a stool normally.

Parental stress *(from additional 9 unmapped outcomes)*	A measure of stress in the parent/guardian that would be measured using a specifically designed questionnaire.
Parent time off work *(added as separate outcome following discussion of updated review, as distinct from parental stress, from 'parent disability days' [1])*	How long a parent/guardian spends away from work.

1. Minneci PC, Mahida JB, Lodwick DL, Sulkowski JP, Nacion KM, Cooper JN, Ambeba EJ, Moss RL, Deans KJ. Effectiveness of Patient Choice in Nonoperative vs Surgical Management of Pediatric Uncomplicated Acute Appendicitis. *JAMA Surg* 2016;**151**(5): 408-415.

Supplementary File 3. Proposed additional outcomes following Delphi round one.

Summary of additional outcomes proposed by participants in round one	**Mapped to existing outcome on long list**	**New outcome created: Yes – plus new outcome name No – plus study team reasoning**
Signs of illness / acuity on blood gases (e.g. raised lactate)	No	No: Not proposed by at least two participants.
If the child continues to be in pain after surgery or suffers any type of abdominal pains continuously.	Pain score; Analgesia (pain relief)	No: Outcome mapped to long list.
Catheterisation/ urinary issues.	No	No: Not proposed by at least two participants.
Bowel habit - constipation due to bowel obstruction/pain; diarrhoea as a marker of intra-abdominal sepsis.	Recovery of bowel function; Other infectious complication.	No: Outcome mapped to long list.
Longer term effects of psychological trauma on patients following emergency surgery.	No	Yes: Psychological distress.
Wrong diagnosis/negative appendicitis.	No	Yes: Negative appendicectomy.
For operative treatment, negative appendicectomy.	No	Yes: Negative appendicectomy.
Nausea and vomiting.	No	No: Not proposed by at least two participants.
Time to return of normal diet.	No	Yes: Time to normal diet.
A proper diagnosis is a good outcome.	No	No: Not classified as an outcome*
More information at local hospitals about the treatment of children with appendicitis. Children's hospital diagnosed very quickly, local hospital were quite unsure and did not seem set up to deal with children who have appendicitis and reluctant to make a diagnosis offering an overnight stay. Children's hospital were much quicker and removed the appendix the same day of admission.	No	No: Not classified as an outcome*

When recovering from appendicitis, I felt pressure in my shoulders and ribs from extra gas in my body. This extra gas was put into my body to keep the organs in place, as the Doctors told me. It is also a very uncomfortable pain that I think is important in terms of recovery, as it stopped me from moving around well/comfortably, and so on.	Pain score; Analgesia (pain relief)	No: Outcome mapped to long list.
Whether girl's fertility would be affected if appendicitis not treated appropriately - this was my concern.	No	No: Not proposed by at least two participants.
Longer term complications including obstruction and chronic pain.	Bowel obstruction; Pain score; Analgesia.	No: Outcome mapped to long list.
The medico-legal aspects must be taken into consideration.	No	No: Not proposed by at least two participants.
Nutritional status.	No	Yes: Time to normal diet.
Multiple operations.	Re-operation	No: Outcome mapped to long list.
Time to eat.	No	Yes: Time to normal diet.
Do we need to do wash out? What antibiotics?	No	No: Not classified as an outcome*
Trauma experience after surgery and the time taken to 'get back to normal'.	No	Yes: Psychological distress.
Total parenteral nutrition (TPN) usage.	No	No: Not proposed by at least two participants.
Surgeon seniority.	No	No: Not classified as an outcome*
Appendix pathway in use.	No	No: Not classified as an outcome*
Ultrasound scan.	Any unplanned imaging	No: Outcome mapped to long list.
Day case (same day discharge).	Hospital length of stay	No: Outcome mapped to long list.

Appendicectomy rates.	No	No: Not classified as an outcome*
Psychological trauma of the patient.	No	Yes: Psychological distress.
Tests parents can do at home to help diagnose appendicitis.	No	No: Not classified as an outcome*
Correct pain relief sent home.	Pain score; Analgesia (pain relief)	No: Outcome mapped to long list.
Weight loss during hospital admission.	No	No: Not proposed by at least two participants.
Anxiety at induction to anaesthetic.	Patient stress	No: Outcome mapped to long list.
Accuracy of pre-operative USS in seeing the appendix and diagnosing appendicitis and if this is used routinely, selectively, or not at all.	No	No: Not classified as an outcome*
A key measure is the negative appendicectomy rate which should be less than 5%.	No	Yes: Negative appendicectomy.
If other imaging modalities are used like MRI and CT and if so, why.	Any unplanned imaging; Unplanned CT scan	No: Outcome mapped to long list.

* We adopted the COMET definition of an outcome,[1] i.e. "An outcome is defined to be a measurement or observation used to capture and assess the effect of treatment such as assessment of side effects (risk) or effectiveness (benefits)."

1. Williamson PR, Altman DG, Bagley H, Barnes KL, Blazeby JM, Brookes ST, Clarke M, Gargon E, Gorst S, Harman N, Kirkham JJ, McNair A, Prinsen CAC, Schmitt J, Terwee CB, Young B. The COMET Handbook: version 1.0. *Trials* 2017;**18**(3): 280.

Supplementary File 4. Outcomes achieving 'consensus in' across the three rounds by each stakeholder group

Table A. Consensus matrix for outcomes rated 'consensus in' by patients across phases

Outcome	Phase one	Phase two	Phase three
Conversion to open operation	✓	✓	
Blood Loss		✓	
Wound infection		✓	✓
Intra-abdominal abscess	✓	✓	✓
Wound complication		✓	
Fever after treatment		✓	✓
Blood markers of inflammation	✓	✓	✓
Other infectious complication		✓	✓
Duration of drainage	✓	✓	✓
Unplanned central venous catheter		✓	✓
Re-operation		✓	✓
Antibiotic failure	✓	✓	✓
Analgesia			✓
Pain score		✓	✓
Readmission to hospital			✓
Bowel obstruction		✓	✓
Major or minor complication		✓	✓
Death	✓	✓	
Time away from school			✓
Time away from full activity			✓
Wound healing time			✓
Child's quality of life	✓	✓	

Cosmesis		✓	✓
Patient stress		✓	
Cost effectiveness		✓	
Bacterial peritoneal cultures		✓	✓
Negative appendicectomy			✓

✓ Indicates where the definition of 'consensus in' was achieved. Grey outcomes highlighted those that were voted 'consensus in' by patients across phases

Table B. Consensus matrix for outcomes rated 'consensus in' by parents across phases

Outcome	**Phase one**	**Phase two**	**Phase three**
Conversion to open operation		✓	
Blood Loss	✓	✓	✓
Wound infection	✓		✓
Intra-abdominal abscess	✓	✓	✓
Wound complication	✓	✓	✓
Fever after treatment	✓	✓	✓
Blood markers of inflammation		✓	
Other infectious complication		✓	
Duration of drainage		✓	
Re-operation	✓	✓	✓
Antibiotic failure	✓	✓	✓
Pain score		✓	✓
Readmission to hospital	✓	✓	✓
Bowel obstruction		✓	✓
Recurrent appendicitis	✓	✓	✓
Major or minor complication		✓	✓

Death	✓	✓	✓
Child's quality of life	✓	✓	✓
Patient stress	✓	✓	✓

✓ Indicates where the definition of 'consensus in' was achieved. Grey outcomes highlighted those that were voted 'consensus in' by parents across phases

Table C. Consensus matrix for outcomes rated 'consensus in' by surgeons across phases

Outcome	**Phase one**	**Phase two**	**Phase three**
Blood Loss		✓	✓
Intra-abdominal abscess	✓	✓	✓
Interventional radiology procedure		✓	✓
Unplanned central venous catheter			✓
Re-operation	✓	✓	✓
Readmission to hospital	✓	✓	✓
Bowel obstruction	✓	✓	✓
Recurrent appendicitis	✓	✓	✓
Major or minor complication	✓	✓	✓
Death	✓	✓	✓
Child's quality of life		✓	✓

✓ Indicates where the definition of 'consensus in' was achieved. Grey outcomes highlighted those that were voted 'consensus in' by surgeons across all three phases

Supplementary File 5. Attrition analyses

Table A. Phase one scores compared between participants who completed phases one and two, and those who completed phase one only.

Outcome	**Phase 1 scores for completed phases 1 and 2, Median (range)**	**Phase 1 scores for completed phase 1 only, Median (range)**
Operation time	6 (1-9)	5 (1-9)
Conversion to open operation	6 (1-9)	5 (2-9)
Blood Loss	7.5 (1-9)	7 (1-9)
Wound infection	7 (1-9)	6 (1-9)
Intra-abdominal abscess	8 (3-9)	8 (2-9)
Wound complication	7 (3-9)	7 (1-9)
Fever after treatment	6 (1-9)	7 (1-9)
Blood markers of inflammation	6 (1-9)	7 (1-9)
Other infectious complication	6 (1-9)	6 (1-9)
Duration of antibiotics	6 (1-9)	6 (1-9)
Recovery of bowel function	6 (1-9)	5 (1-9)
Time to ambulation	6 (1-9)	6 (3-9)
Hospital length of stay	6 (1-9)	7 (3-9)
Duration of drainage	6 (1-9)	6 (1-9)
Unplanned CT scan	5 (1-9)	5.5 (1-9)
Any unplanned imaging	5 (1-9)	5 (1-9)
Interventional radiology procedure	6 (1-9)	5 (1-9)
Unplanned central venous catheter	7 (1-9)	5 (1-9)
Re-operation	8 (1-9)	8 (1-9)
Antibiotic failure	7 (1-9)	8 (3-9)
Analgesia	6 (1-9)	5 (1-9)
Pain score	6 (2-9)	6 (1-9)
Readmission to hospital	7 (4-9)	7 (3-9)
Bowel obstruction	8 (3-9)	7 (3-9)
Recurrent appendicitis	8 (3-9)	8 (1-9)
Major or minor complication	8 (3-9)	8 (3-9)
Death	9 (1-9)	9 (3-9)
Time away from school	6 (1-9)	6 (1-9)
Time away from full activity	6 (1-9)	6 (2-9)
Parent time off work	5 (1-9)	6 (1-9)
Wound healing time	6 (1-9)	6 (3-9)
Child's quality of life	7 (1-9)	7 (3-9)
Cosmesis	5 (1-9)	5 (1-9)
Parental stress	5 (1-9)	5 (1-9)
Patient stress	7 (1-9)	6 (1-9)
Total cost of treatment	5 (1-9)	5 (1-9)
Cost effectiveness	6 (1-9)	6 (1-9)
Total healthcare visits	5 (1-9)	5 (1-9)
Duration of home healthcare	5 (1-9)	6 (1-9)
Bacterial peritoneal cultures	5 (1-9)	5 (1-9)

Figure A. Phase one scores between participants who completed phases one and two (green), and those who completed phase one only (blue).

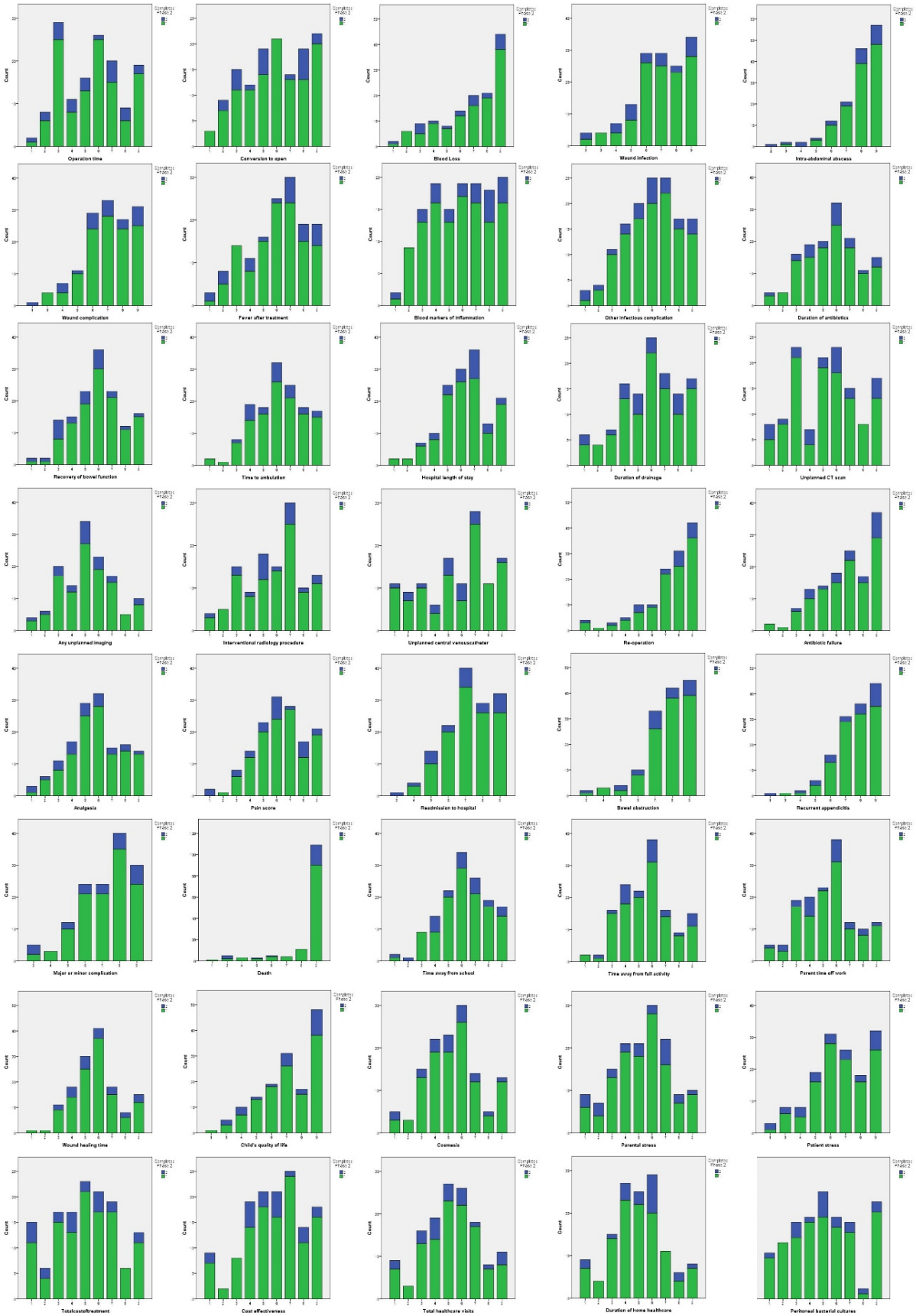


Table B. Phase one scores compared between participants who completed phases one and three, and those who completed phase one only.

Outcome	**Phase 1 scores for completed phases 1 and 3, Median (range)**	**Phase 1 scores for completed phase 1 only, Median (range)**
Operation time	6 (2-9)	6 (1-9)
Conversion to open operation	6 (1-9)	6 (1-9)
Blood Loss	7 (1-9)	7 (1-9)
Wound infection	7 (1-9)	7 (1-9)
Intra-abdominal abscess	8 (3-9)	8 (2-9)
Wound complication	7 (3-9)	7 (1-9)
Fever after treatment	6 (1-9)	7 (1-9)
Blood markers of inflammation	5 (1-9)	7 (1-9)
Other infectious complication	6 (1-9)	6 (1-9)
Duration of antibiotics	6 (1-9)	6 (1-9)
Recovery of bowel function	6 (1-9)	6 (1-9)
Time to ambulation	6 (1-9)	6 (3-9)
Hospital length of stay	6 (1-9)	7 (2-9)
Duration of drainage	6 (1-9)	6 (1-9)
Unplanned CT scan	5.5 (1-9)	5 (1-9)
Any unplanned imaging	5 (1-9)	5 (1-9)
Interventional radiology procedure	6 (1-9)	6 (1-9)
Unplanned central venous catheter	6 (1-9)	6 (1-9)
Re-operation	8 (1-9)	8 (1-9)
Antibiotic failure	7 (1-9)	7 (1-9)
Analgesia	6 (2-9)	6 (1-9)
Pain score	6 (2-9)	6 (1-9)
Readmission to hospital	7 (4-9)	7 (3-9)
Bowel obstruction	8 (3-9)	7 (3-9)
Recurrent appendicitis	8 (3-9)	8 (1-9)
Major or minor complication	7.5 (3-9)	8 (3-9)
Death	9 (1-9)	9 (3-9)
Time away from school	6 (3-9)	7 (1-9)
Time away from full activity	6 (1-9)	6 (1-9)
Parent time off work	5 (1-9)	6 (1-9)
Wound healing time	6 (2-9)	6 (1-9)
Child's quality of life	7 (3-9)	7 (1-9)
Cosmesis	5 (2-9)	5 (1-9)
Parental stress	6 (1-9)	5 (1-9)
Patient stress	7 (3-9)	7 (1-9)
Total cost of treatment	5 (1-9)	5 (1-9)
Cost effectiveness	6 (1-9)	6 (1-9)
Total healthcare visits	5 (1-9)	5 (1-9)
Duration of home healthcare	5 (1-9)	5 (1-9)
Bacterial peritoneal cultures	5 (1-9)	5 (1-9)

Figure B. Phase one scores in participants who completed phases one and three (green), and those who completed phase one only (blue)