Identification of the optimal treatment strategy for complex appendicitis in the paediatric population: a protocol for a multicentre prospective cohort study (CAPP study)

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ABSTRACT
Introduction
In daily practice large heterogeneity in the treatment of children with complex appendicitis exists. Complex appendicitis can be divided into two subtypes; complex appendicitis with and without appendiceal mass and/or abscess. As complex appendicitis is associated with high morbidity and costs, identification of the optimal treatment strategy is essential. In this article, we present the study protocol for the CAPP (Complex Appendicitis in the Pediatric Population) study.

Methods and analysis
This nation-wide, multi-centre, comparative, non-randomised prospective cohort study includes all children <18 years old with a preoperative suspicion of complex appendicitis, which is based on imaging confirmed acute appendicitis and predefined criteria regarding the severity of appendicitis. Eligible patients are recruited in more than 30 hospitals. Open appendectomy will be compared with laparoscopic appendectomy for children without appendiceal mass and/or abscess and initial non-operative treatment (ie, intravenous antibiotics with or without percutaneous drainage) to direct appendectomy for children with appendiceal mass and/or abscess. Based on historical data supplied by the participating hospitals and an inclusion period of 2 years and 9 months, a sample size of 1308 patients is aimed. Primary outcome is the proportion of patients experiencing any complication at 3 months follow-up. Reported complications will be assessed by an independent adjudication committee. Secondary outcomes include, but are not limited to, quality of life, and (in)direct costs. To adjust for baseline differences and selection bias, outcomes will be compared after propensity score analysis (inverse probability weighting and stratification).

Ethics and dissemination
The Medical Ethics Review Committee of the Amsterdam UMC, location AMC, declared that the Medical Research involving Human Subjects Act (WMO) did not apply to this study. Therefore, no official approval was required by national law. Study results will be presented in peer-reviewed scientific journals and at (international) conferences.

Trial registration numbers
NCT04755179; NL9371.

Strengths and limitations of this study
- Generalisable data were gathered from a large cohort of children treated for acute complex appendicitis according to standardised treatment strategies in more than 30 academic and (large) teaching hospitals in the Netherlands.
- Study protocol designed by a multidisciplinary team consisting of epidemiologists, paediatricians, infectiologists, gastroenterologists, (interventional) radiologists, patient support groups and (paediatric) surgeons.
- Assessment of all complications and severity by an independent adjudication committee.
- Although identified confounders will be taken into account in a propensity score analysis, the non-randomised study design potentially allows for confounding by indication.

INTRODUCTION
Acute appendicitis is one of the most common gastrointestinal disorders with a lifetime incidence of 7%–9%. It is frequently encountered in children, as in the Netherlands approximately one-third of all patients with acute appendicitis are under the age of 20 years. Insights in the pathogenesis of appendicitis have led to the recognition of two distinct types: simple (or uncomplicated) and complex (or complicated) appendicitis. Current research projects worldwide mainly focus on the treatment of simple appendicitis questioning the necessity of appendectomy. However, in daily clinical practice large heterogeneity exists in the treatment of complex appendicitis, a disease that is associated with morbidity in up to 30% of patients, prolonged hospital stay and high costs. Identification of the optimal treatment of complex appendicitis
is therefore essential. Complex appendicitis can be divided into two subtypes: complex appendicitis without mass and/or abscess formation and complex appendicitis with mass and/or abscess formation.

Although (inter)national guidelines agree that appendectomy is recommended for children presenting with complex appendicitis without appendiceal mass and/or abscess, the optimal surgical approach (laparotomy or laparoscopy) is unclear. In recent times laparoscopic appendectomy is increasingly applied in both adults (80%) and children (60%). Potential benefits reported for this approach (compared with open appendectomy) are, but not limited to, less superficial site infection, reduced length of hospital stay and less postoperative bowel obstruction. The presumed higher incidence of postoperative intra-abdominal abscess formation seems the reason that some surgeons are reluctant to use the laparoscopic approach. However, the level of evidence on this topic is low and inconsistency in results is found between studies.

Evidence regarding the treatment of children presenting with complex appendicitis with mass and/or abscess formation is scarce as well. Some surgeons favour direct appendectomy, whereas others prefer an initial non-operative approach consisting of intravenous antibiotics with or without (percutaneous) abscess drainage. A Cochrane review only included two randomised controlled trials and stated that no firm conclusions could be drawn on the optimal treatment (direct appendectomy or initial non-operative treatment) of children with complex appendicitis with mass and/or abscess formation. Another systematic review, including seven historical cohort studies that reported on cohorts of children that were treated either non-operatively or by direct appendectomy, concluded that non-operative treatment led to fewer complications, specifically superficial site infection and postoperative intra-abdominal abscess formation, compared with direct appendectomy. Contrarily, the Dutch national guideline (2019) for the diagnosis and management of appendicitis recommends to perform direct appendectomy in children, which is purely based on expert opinion.

The lack of high-quality data regarding the management of complex appendicitis in the paediatric population emphasises the need for well-designed studies in order to identify the optimal treatment strategy for complex appendicitis in the paediatric population. The aim of this study is twofold; first, to evaluate the outcomes (in terms of complications, health-related quality of life (HRQoL) and costs) of open appendectomy compared with laparoscopic appendectomy for children with complex appendicitis without appendiceal mass and/or abscess. Second to compare the outcomes (in terms of complications, HRQoL and costs) of initial non-operative treatment (ie, intravenous antibiotics with or without percutaneous drainage) with direct appendectomy for children with complex appendicitis with appendiceal mass and/or abscess. Here, we present the protocol for this observational study, registered at Clinical-Trials.gov on 29 January 2021 and the Netherlands Trial Register on 4 April 2021.

METHODS AND ANALYSIS

Study design and patient involvement

‘The identification of the optimal treatment strategy for Complex Appendicitis in the Pediatric Population’ (CAPP) study is a nationwide, multi-centre, comparative, non-randomised prospective cohort study with standardised treatment strategies. The choice of treatment is jointly decided by the physician and the patient/parents, and subsequently a standardised treatment strategy is followed. Data are collected during admission, at 1 and 3 months after inclusion.

Patients, parents and patient support groups were involved at several stages of the study design. The Dutch Foundation Child and Hospital advised on study design, supported protocol drafting and will be involved in dissemination of the main results of this study to participants and public. Outcome measures for this study were determined according to the core outcome set for clinical trials investigating any treatment of acute simple appendicitis. Patients and parents were involved in focus groups and consensus meetings in which the core outcome set was developed.

Patient selection

Eligible for inclusion are all children <18 years old that need to undergo treatment for the suspicion of complex appendicitis. Preoperative suspicion of complex appendicitis is based on imaging confirmed acute appendicitis and the following predefined criteria (regarding the severity of appendicitis):

- Four points or more on the complex appendicitis prediction score.
- OR
- High suspicion of complex appendicitis by the treating physician. In this case, the treating physician is requested to record (before treatment) the clinical, biochemical or radiological variable underlying the suspicion.

Complex appendicitis prediction score

The complex appendicitis prediction score is a paediatric scoring system that predicts the probability of complex appendicitis. This scoring system with a scale ranging from 0 to 10, consists of five preoperative variables (each awarded points): diffuse abdominal guarding (three points), C-reactive protein level >38 mg/L (two points), signs of complex appendicitis on ultrasound (two points), temperature >37.5°C (one point) and more than 1 day of abdominal pain (two points). In an independent validation in a paediatric cohort, this scoring system had a diagnostic accuracy of 91% (95% CI 84% to 98%), 90% (95% CI 54% to 99%) sensitivity, 91% (95% CI 79% to 97%) specificity, positive likelihood ratio of 10 (95% CI 4.19 to 23.42) and negative likelihood ratio of 0.11 (95% CI 0.02 to 0.71).

Subgroups of complex appendicitis

Patients will be classified into the two subgroups of complex appendicitis based on clinical and radiological...
features. If no enlarged mass is found during physical examination and no appendiceal abscess is present on additional imaging, patients will be categorised as subgroup 1 (complex appendicitis without abscess or mass). In this subgroup laparoscopic appendectomy will be compared with open appendectomy. If signs suggestive of intra-abdominal abscess and/or enlarged mass are present, patients will be categorised as subgroup 2 (complex appendicitis with abscess or mass). Initial non-operative treatment will be compared with direct appendectomy (laparoscopic or open) in this subgroup. See figure 1 for a flowchart displaying the management strategies.

Study setting and feasibility
Eligible patients are recruited in more than 30 hospitals, both academic and large peripheral teaching hospitals, across the Netherlands. Inclusion started on 12 August 2019.

Based on data supplied by the participating hospitals, approximately 634 children per year are expected to meet the inclusion criteria. As this is an observational study, we expect a participation rate of 75%. Taking into account an inclusion period of 2 years and 9 months we expect 1308 children to participate in this study.

The expected distribution of patients with complex appendicitis without abscess/mass (subgroup 1) and patients with abscess/mass (subgroup 2) is 75% versus 25%. Thus it is expected that 981 children will be included in subgroup 1 and 327 in subgroup 2.

Diagnostic work-up and treatment of all children with complex appendicitis will be in line with the recommendations of the Dutch national guideline.

Sample size calculation
Based on the expected inclusion of 981 children with complex appendicitis without abscess/mass and assuming a distribution of open versus laparoscopic surgery of 40% versus 60%, an absolute difference in overall complications of 7.3% between the two treatment strategies can be detected with a power of 80% and a significance level of 5%. This difference in overall complications would be clinically relevant, and if detected in this study, would
lead to changes in surgical approach for children with complex appendicitis without mass and/or abscess.

As described, it is expected that 327 children with complex appendicitis with abscess/mass formation will be included in the CAPP study. With 327 included patients in subgroup 2 and assuming a distribution of non-operative treatment versus direct appendectomy of 20% versus 80%, an absolute difference in overall complications of 16.4% between the treatment strategies can be detected with a power of 80% and a significance level of 5%. If detected, this difference would be clinically relevant, leading to changes in the standard treatment strategy for children with appendiceal mass and/or abscess.

Standardised treatment strategies

Standardised treatment protocols were developed in order to reduce the heterogeneity in treatment between the participating hospitals. All participating sites agreed to conform to these standardised treatment protocols to the best of their ability. These standardised treatments are completely based on the recommendations given in the Dutch national guideline regarding the preoperative, perioperative and postoperative care. See table 1, Box 1, and online supplemental appendix 1 for a detailed description of the treatment strategies. All key points of the treatment strategies that are described in table 1, Box 1, and online supplemental appendix 1 are recommendations of the Dutch national guideline.

### Study outcomes

#### Primary outcome

The primary outcome is defined as the proportion of patients experiencing any complication within 3 months after inclusion. An independent adjudication committee will review all reported complications to determine whether or not they meet the definition of complications and to assess their relation to treatment. This committee will categorise all complications according to the Clavien-Dindo scale.16

The following events will be considered as complications, but the list is not exhaustive:

- Superficial site infection: criteria according to the CDC guidelines.17
- Intra-abdominal abscess: radiologically confirmed fluid collection containing pus or infected material that is surrounded by inflamed tissue.
- Stump leakage: radiologically confirmed intra-abdominal fluid collections after appendectomy.
- Stump appendicitis: radiologically confirmed recurrence of disease after appendectomy.
- Secondary/prolonged bowel obstruction (including paralytic ileus) confirmed by imaging or perioperative diagnosis with the need for treatment. For instance, a patient requiring gastrointestinal decompression with a nasogastric tube.
- Anaesthesia-related complications, such as pneumonia.
- Incisional hernia: any abdominal wall gap with or without a bulge in the area of a postoperative scar.

### Table 1 Key points standardised treatment strategies

| Laparoscopic appendectomy | Open appendectomy | Non-operative treatment |
|---------------------------|-------------------|-------------------------|
| Conventional laparoscopy (three-trocar technique) | Gridiron incision at McBurney | At least 48 hours of intravenous antibiotics (type of antibiotics according to local protocol) |
| Only suction and no peritoneal lavage in case of purulent fluid | Abdominal wall protection after obtaining access to the abdominal cavity | Clinical evaluation of vital parameters every 8 hours |
| Treatment of the mesoappendix with coagulation or clips | Appendiceal stump closure by ligation | The decision to perform percutaneous/surgical drainage of an appendiceal abscess is made by the treating surgeon |
| Appendiceal stump closure: Two endoloops. In case of involvement of the appendiceal base, the use of endostapler is recommended. | Closure of wounds as appropriate | Prior to removal of the drainage tube, imaging studies will be obtained to confirm the resolution of the abscess |
| Withdrawal of appendix through trocar or with an endobag | Drains, nasogastric tubes and urinary catheters are not routinely placed, only on indication |

### Box 1 Predefined discharge criteria

**Discharge criteria equal for all treatment strategies**
- Body temperature <38°C.
- NRS <4.
- Adequate oral intake.
- Able to mobilise.

**Additional discharge criteria for non-operative treatment strategy**
- Decreased leucocytosis.
- Decreased C-reactive protein.
- NRS, Numeric Rating Scale.
perceptible or palpable by clinical examination or imaging.

- Need for additional surgical or radiological interventions related to the primary disease (appendicitis).
- Readmission for an indication related to appendicitis.
- Such as readmissions for recurrent/residual appendicitis, and clinical observation of fever and abdominal pain.

Secondary outcomes
Follow-up will take place at 30 days and 3 months after inclusion to evaluate the secondary outcomes. The secondary outcomes of this study are listed below.

Treatment-related endpoints

- Proportion of patients experiencing any complication during admission.
- Proportion of patients experiencing any complication within 30 days after inclusion.
- Proportion of patients with a postoperative intra-abdominal abscess within 3 months after inclusion.
- Proportion of patients with a superficial site infection within 3 months after inclusion.
- Proportion of patients with a secondary/prolonged bowel obstruction within 3 months after inclusion.
- Proportion of patients not having to undergo appendectomy within 3 months after inclusion.
- Proportion of patients experiencing recurrent appendicitis within 3 months after inclusion (histopathologically confirmed).
- Proportion of patients experiencing early failure of non-operative treatment, defined as those patients that undergo appendectomy during the antibiotic course (intravenous or oral) due to persistent complaints, clinical deterioration or faecolith.
- Proportion of patients that undergo interval appendectomy within 3 months after inclusion (histopathologically no sign of recurrent appendicitis).

Patient-related endpoints

- Level of pain: assessed by the Numeric Rating Scale and total use of pain medication during admission.
- Health-related Quality of Life (Hr-QoL) measured by the validated European Quality of Life-5 Dimensions-Youth, European Quality of Life-5 Dimensions-Proxy questionnaires and Pediatric Quality of Life Inventory 4.0 at admission, 30 days and 3 months after inclusion.18 19
- Patient satisfaction measured by the Net Promoter Score and the validated Patient Satisfaction Questionnaire (PSQ-18).20
- Number of days absent from school, social or sport events (patient level).
- Number of days absent from work (parent level).
- Total number of extra visits (not the already scheduled ones) to the outpatient clinic, general practitioner’s office or emergency department for abdominal pain within 3 months after inclusion.
- Total length of hospital stay during follow-up period for strategy related treatment or complications.

Cost-related endpoints

- Non-medical and indirect costs until 3 months after inclusion measured by the Medical Consumption Questionnaire (iMCQ) and the Productivity Cost Questionnaire (iPCQ) adapted for use in children and parents.21 22
- Direct (actual) healthcare costs measured by variables such as number of outpatient visits, in-hospital generated costs, number of general practitioner visits, and number of emergency department visits.

Statistical analysis plan

General principles
Analysis of the primary and secondary outcomes will be performed after the final follow-up moment of the last patient, and after data cleaning for these outcomes has been completed. Recruitment of patients will be presented using a flow diagram as shown in figure 2.

For the primary analysis all patients with a preoperative diagnosis of complex appendicitis will be included. Subsequently only patients with a perioperative and/or histopathologically confirmed complex appendicitis as classified by the criteria proposed by Bhangu et al, will be included in a secondary analysis.23 Furthermore, patients with complex appendicitis with mass and/or abscess (subgroup 2) that are treated by direct appendectomy will be divided by surgical approach (laparoscopic or open) in a secondary analysis in order to investigate the influence of surgical approach on primary and secondary outcomes in this subgroup.

To estimate the effect of treatments, adjusted for potential confounders, a propensity score method will be applied in both subgroups.24 Directed Acyclic Graphs (DAGs) were created to identify potential patient-related confounding variables (figures 3 and 4). Identified variables for subgroup 1 are age, body mass index (BMI), comorbidity, ASA classification, preoperative systemic inflammatory response syndrome, time of presentation (day/night and weekday/weekend), duration of abdominal pain, and the surgeon’s preference for one of both treatment strategies. For subgroup 2 age, BMI, comorbidity, preoperative systemic inflammatory response syndrome, time of presentation (day/night and weekday/weekend), size of the abscess on imaging and the surgeon’s preference for one of both treatment strategies were found to be the most important potential confounding variables. These variables will be collected preoperatively using standardised forms. Inverse probability of treatment weighting (IPTW) will be applied to estimate treatment effect adjusted for the identified covariates. Subsequently, sensitivity analysis will be performed by propensity score stratification, in which each patient will be classified into one of the five equally sized propensity score strata. The strata are formed by the quintiles of the observed propensity
score distribution. The treatment effect and its variance will be estimated in each stratum. Effects and variances will then be pooled by taking their average across strata.

We will examine the overlap of propensity scores in the treatment groups as well as the balancing property of propensity scores. To examine overlap, the empirical distributions of the linearised propensity score will be compared between treatment groups. Balancing will be assessed by comparing the standardised differences in covariates in means for continuous variables and in percentages for dichotomous variables within (a) the groups obtained after IPTW and (b) each propensity score stratum. Insignificant differences (p<0.05) or low standardised mean differences (<0.1) support the assumption of balance between the treatment groups.\(^{25 \ 26}\)

**Baseline characteristics**

Baseline characteristics will be presented for the total population (patients with a preoperative suspicion of complex appendicitis) as treated, using the format as presented in tables 2 and 3. Data will be presented using absolute numbers and percentages for discrete outcomes. Continuous outcomes will be presented as means with SD or medians with IQRs, according to their distribution. Baseline characteristics will be compared between treatment groups and presented for both the prematching cohort and postmatching cohort. For each subgroup of complex appendicitis a baseline characteristics table will be created.

**Primary endpoint analysis**

Proportion of complications after 3 months will be compared for both subgroups of preoperatively suspected complex appendicitis (subgroup 1 and 2 as described). Data on the primary outcome will be presented as shown in tables 4 and 5.

Unadjusted and propensity score adjusted differences in proportions and ORs will be presented with their 95% CIs.
Secondary endpoints analysis
Data on the secondary outcomes will be presented as displayed in tables 6 and 7. Unadjusted and propensity score adjusted ORs and mean differences for continuous outcomes will be presented with their 95% CI.

Cost-effectiveness analysis
In this study, cost-effectiveness and cost-utility will be assessed. Utility will be measured by the EQ-5D-Proxy, and EQ-5D-Y at admission, 1 month, and 3 months. In this way both the child’s and parents’ perspective will be assessed. No difference in effect is anticipated after 3 months, as acute appendicitis is an acute disease with a relatively short period of disutility.

Costs will be assessed from the societal perspective, integrating healthcare costs and societal costs (loss of productivity). Integrated costs, consisting of direct medical costs, indirect medical costs and indirect costs, will be evaluated for each treatment strategy. For this purpose, data will be gathered by iMCQ and iPCQ questionnaires at admission and 3 months. In addition, secondary data will be gathered from the patients’ medical chart and financial information system from the participating hospitals. Adjustment for inflation will be made using the price-index-indices as provided by statline.cbs.nl.

Outcome analysis
In the cost-effectiveness analysis, the incremental cost-effectiveness ratio (ICER) will be calculated representing the difference in costs between the two treatments relative to the difference in the proportion of patients with a complication. Next to the ICER, net monetary benefit will

Figure 3  Direct Acyclic Graph subgroup 1. ASA, American Society of Anesthesiologists. BMI, Body Mass Index. SIRS, Systemic Inflammatory Response Syndrome.

Figure 4  Direct Acyclic Graph subgroup 2. BMI, Body Mass Index. SIRS, Systemic Inflammatory Response Syndrome.
## Table 2  
Baseline characteristics subgr oup 1

| Variable                        | Preweighting sample | Postweighting sample | P value | Preweighting sample | Postweighting sample | P value |
|--------------------------------|---------------------|----------------------|---------|---------------------|----------------------|---------|
|                                | Laparoscopic appendectomy, n | Open appendectomy, n |         | Laparoscopic appendectomy, n | Open appendectomy, n |         |
| Age, n (%)                     |                     |                      |         |                     |                      |         |
| 0–5                            | N (% of total)      | N (% of total)       | p=0.XX  | N (% of total)      | N (% of total)       | p=0.XX  |
| 6–11                           | N (% of total)      | N (% of total)       | p=0.XX  | N (% of total)      | N (% of total)       | p=0.XX  |
| 12–17                          | N (% of total)      | N (% of total)       | p=0.XX  | N (% of total)      | N (% of total)       | p=0.XX  |
| Sex, n (%)                     |                     |                      |         |                     |                      |         |
| Female                         | N (% of total)      | N (% of total)       | p=0.XX  | N (% of total)      | N (% of total)       | p=0.XX  |
| Male                           | N (% of total)      | N (% of total)       | p=0.XX  | N (% of total)      | N (% of total)       | p=0.XX  |
| BMI Mean (SD)                  |                     |                      |         |                     |                      |         |
| Comorbidities, n (%)           |                     |                      |         |                     |                      |         |
| Abdominal surgery              | N (% of total)      | N (% of total)       | p=0.XX  | N (% of total)      | N (% of total)       | p=0.XX  |
| Abdominal (non-surgical)       | N (% of total)      | N (% of total)       | p=0.XX  | N (% of total)      | N (% of total)       | p=0.XX  |
| Cardiopulmonary                | N (% of total)      | N (% of total)       | p=0.XX  | N (% of total)      | N (% of total)       | p=0.XX  |
| Neurological                   | N (% of total)      | N (% of total)       | p=0.XX  | N (% of total)      | N (% of total)       | p=0.XX  |
| Metabolical                    | N (% of total)      | N (% of total)       | p=0.XX  | N (% of total)      | N (% of total)       | p=0.XX  |
| Nefro/urological               | N (% of total)      | N (% of total)       | p=0.XX  | N (% of total)      | N (% of total)       | p=0.XX  |
| Endocrinological               | N (% of total)      | N (% of total)       | p=0.XX  | N (% of total)      | N (% of total)       | p=0.XX  |
| Musculoskeletal                | N (% of total)      | N (% of total)       | p=0.XX  | N (% of total)      | N (% of total)       | p=0.XX  |
| Other                          | N (% of total)      | N (% of total)       | p=0.XX  | N (% of total)      | N (% of total)       | p=0.XX  |
| ASA score, n (%)               |                     |                      |         |                     |                      |         |
| ASA I                          | N (% of total)      | N (% of total)       | p=0.XX  | N (% of total)      | N (% of total)       | p=0.XX  |
| ASA II                         | N (% of total)      | N (% of total)       | p=0.XX  | N (% of total)      | N (% of total)       | p=0.XX  |
| ASA III                        | N (% of total)      | N (% of total)       | p=0.XX  | N (% of total)      | N (% of total)       | p=0.XX  |
| ASA IV                         | N (% of total)      | N (% of total)       | p=0.XX  | N (% of total)      | N (% of total)       | p=0.XX  |
| ASA V                          | N (% of total)      | N (% of total)       | p=0.XX  | N (% of total)      | N (% of total)       | p=0.XX  |
| Preoperative SIRS, n (%)       |                     |                      |         |                     |                      |         |
| Complex appendicitis prediction score | Mean (SD) | Mean (SD) | p=0.XX | Mean (SD) | Mean (SD) | p=0.XX |
| Preference for treatment strategy |                     |                      |         |                     |                      |         |
| Surgeon                        | N (% of total)      | N (% of total)       | p=0.XX  | N (% of total)      | N (% of total)       | p=0.XX  |
| Parent(s)                      | N (% of total)      | N (% of total)       | p=0.XX  | N (% of total)      | N (% of total)       | p=0.XX  |
| Patient                        | N (% of total)      | N (% of total)       | p=0.XX  | N (% of total)      | N (% of total)       | p=0.XX  |
| Preoperative imaging, n (%)    |                     |                      |         |                     |                      |         |
| US                             | N (% of total)      | N (% of total)       | p=0.XX  | N (% of total)      | N (% of total)       | p=0.XX  |
| US+MRI                         | N (% of total)      | N (% of total)       | p=0.XX  | N (% of total)      | N (% of total)       | p=0.XX  |
| US+CT                          | N (% of total)      | N (% of total)       | p=0.XX  | N (% of total)      | N (% of total)       | p=0.XX  |
| Hospital, n (%)                |                     |                      |         |                     |                      |         |
| Academic                       | N (% of total)      | N (% of total)       | p=0.XX  | N (% of total)      | N (% of total)       | p=0.XX  |
| Teaching                       | N (% of total)      | N (% of total)       | p=0.XX  | N (% of total)      | N (% of total)       | p=0.XX  |
| Non-teaching                   | N (% of total)      | N (% of total)       | p=0.XX  | N (% of total)      | N (% of total)       | p=0.XX  |
| Daytime presentation, n (%)    |                     |                      |         |                     |                      |         |

Continued
be calculated for the treatment strategies, expressing the uncertainty in average costs and effects.

In the cost–utility analyses, the effect of the new treatment is measured by the change in number of QALYs. The ICER will be evaluated against a threshold of €20000/QALY. QALY’s will be calculated using the EQ-5D youth and EQ-5D-Proxy questionnaires. As acute appendicitis is an acute disease, disability might be short-term in our study. Therefore, QALY’s will be transformed to quality-adjusted life months.

**Budget impact analysis**

**General considerations**

Budget impact analysis (BIA) will be performed from the budget holders’ perspective, which is the healthcare insurance company. Time-frame will be 5 years as we expect, despite maximum effort, implementation needs some time. Data will be displayed each year taking into account the anticipated market penetration/implementation of the new identified optimal strategies and de-implementation of the current ones. Aim is to predict the effects on budgets after implementation of these new strategies from the stakeholders’ perspective (ie, healthcare professionals, patients and parents, and insurance companies).

**Cost analysis**

Identification of all healthcare related costs will be recorded per patient. Potential determinants influencing the BIA such as complications and influence of own risk will be taken into account. Indirect non-medical costs (societal/patients perspective) will not be included in this BIA and no discounted costs will be calculated. Total costs will then be calculated for each treatment strategy at 3 months. A simple cost-calculator programmed in a spreadsheet will be used in which obtained data is inserted. At completion of this study, based on a parallel problem analysis study of implementation an estimation of the degree of implementation per year will be done. Uncertainty will be taken into account (both in input values (efficacy) and in structural values (implementation)). Multiple scenario analyses will be undertaken to produce plausible alternative scenarios to anticipate this. Total costs prior to and after implementation of the preferred strategy will be calculated and displayed as total impact of the new strategy on the healthcare budget per annum for the Netherlands in terms of cost reduction.

**Data and dissemination**

**Data collection and confidentiality**

A unique code is assigned to every participant of the study. Personal data will not be identifiable through these codes. The encryption key containing the study code and patient identification information is only accessible by the principal investigator. Data are handled confidentially in accordance with the General Data Protection Regulation. Castor Electronic Data Capture will be used for data collection and storage. This is a web-based electronic database with audit trail. Data collection through electronic case record forms, data analysis and data storage will follow the Good Clinical Practice guidelines. Deidentified data will be stored for at least 15 years. Source data verification will be performed by on-site monitoring of participating sites by an independent and qualified monitor.

**Ethics and dissemination**

**Ethics**

The Medical Ethics Review Committee of the Amsterdam UMC, location AMC, declared that the Medical Research Involving Human Subjects Act did not apply to this study and, therefore, no official approval was required by national law. The study will be conducted according to the directives of the ICH Good Clinical Practice guidelines and the Declaration of Helsinki.

**Withdrawal**

Participants are allowed to withdraw their permission for their data usage at any time without explanation. Data of these patients will not be used in our analysis.

**Dissemination plan**

Results of this study will be submitted to an international peer-reviewed scientific journal and for presentation at (inter)national conferences. The results of this study may lead to novel insights into the treatment of complex appendicitis in the paediatric population. If these novel insights warrant changes in the national guidelines for the treatment of complex appendicitis, the nationwide (design and) conduct of the study will aid in its implementation. Furthermore, we will perform an implementation study parallel to this observational study.

**Implementation study**

A parallel impact analysis study will be performed to identify promoting and obstructing factors for

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Table 2

| Variable                              | Prewighting sample | Postweighting sample |
|---------------------------------------|--------------------|----------------------|
|                                       | Laparoscopic       | Open                 | P value | Laparoscopic | Open |
|                                       | appendectomy, n    | appendectomy, n     |         | appendectomy, n | appendectomy, n |
| Weekend presentation, n (%),          | N (% of total)     | N (% of total)       | p=0.2X  | N (% of total) | N (% of total) |
| Duration of abdominal pain, Median (IQR) |        | Median (IQR)        | p=0.2X  | Median (IQR) | Median (IQR) |

ASA, American Society of Anesthesiologists; BMI, Body Mass Index; SIRS, Systemic Inflammatory Response Syndrome.
| Variable                      | Preweighting sample | Postweighting sample | P value | Preweighting sample | Postweighting sample | P value |
|------------------------------|---------------------|----------------------|---------|---------------------|----------------------|---------|
|                             | Non-operative       | Direct appendectomy, |         | Non-operative       | Direct appendectomy, |         |
|                             | treatment, n        | n                    | p        | treatment, n        | n                    | p        |
| Age, n (%)                  |                     |                      |          |                     |                      |         |
| 0–5                         | N (% of total)       | N (% of total)       | p=0.XX   | N (% of total)       | N (% of total)       | p=0.XX   |
| 6–11                        | N (% of total)       | N (% of total)       | p=0.XX   | N (% of total)       | N (% of total)       | p=0.XX   |
| 12–17                       | N (% of total)       | N (% of total)       | p=0.XX   | N (% of total)       | N (% of total)       | p=0.XX   |
| Sex, n (%)                  |                     |                      |          |                     |                      |         |
| Female                      | N (% of total)       | N (% of total)       | p=0.XX   | N (% of total)       | N (% of total)       | p=0.XX   |
| Male                        | N (% of total)       | N (% of total)       | p=0.XX   | N (% of total)       | N (% of total)       | p=0.XX   |
| BMI Mean (SD)               |                     |                      |          |                     |                      |         |
| Comorbidities, n (%)        |                     |                      |          |                     |                      |         |
| Abdominal surgery           | N (% of total)       | N (% of total)       | p=0.XX   | N (% of total)       | N (% of total)       | p=0.XX   |
| Abdominal (non-surgical)    | N (% of total)       | N (% of total)       | p=0.XX   | N (% of total)       | N (% of total)       | p=0.XX   |
| Cardiopulmonary             | N (% of total)       | N (% of total)       | p=0.XX   | N (% of total)       | N (% of total)       | p=0.XX   |
| Neurological                | N (% of total)       | N (% of total)       | p=0.XX   | N (% of total)       | N (% of total)       | p=0.XX   |
| Metabolic                   | N (% of total)       | N (% of total)       | p=0.XX   | N (% of total)       | N (% of total)       | p=0.XX   |
| Nefro/urological            | N (% of total)       | N (% of total)       | p=0.XX   | N (% of total)       | N (% of total)       | p=0.XX   |
| Endocrinological            | N (% of total)       | N (% of total)       | p=0.XX   | N (% of total)       | N (% of total)       | p=0.XX   |
| Musculoskeletal             | N (% of total)       | N (% of total)       | p=0.XX   | N (% of total)       | N (% of total)       | p=0.XX   |
| Other                       | N (% of total)       | N (% of total)       | p=0.XX   | N (% of total)       | N (% of total)       | p=0.XX   |
| ASA score, n (%)            |                     |                      |          |                     |                      |         |
| ASA I                       | N (% of total)       | N (% of total)       | p=0.XX   | N (% of total)       | N (% of total)       | p=0.XX   |
| ASA II                      | N (% of total)       | N (% of total)       | p=0.XX   | N (% of total)       | N (% of total)       | p=0.XX   |
| ASA III                     | N (% of total)       | N (% of total)       | p=0.XX   | N (% of total)       | N (% of total)       | p=0.XX   |
| ASA IV                      | N (% of total)       | N (% of total)       | p=0.XX   | N (% of total)       | N (% of total)       | p=0.XX   |
| ASA V                       | N (% of total)       | N (% of total)       | p=0.XX   | N (% of total)       | N (% of total)       | p=0.XX   |
| Preoperative SIRS, n (%)    |                     |                      |          |                     |                      |         |
| Complex appendicitis        |                     |                      |          |                     |                      |         |
| prediction score            | Mean (SD)            | Mean (SD)            | p=0.XX   | Mean (SD)            | Mean (SD)            | p=0.XX   |
| Preference for treatment    |                     |                      |          |                     |                      |         |
| strategy                    |                      |                      |          |                     |                      |         |
| Surgeon                     | N (% of total)       | N (% of total)       | p=0.XX   | N (% of total)       | N (% of total)       | p=0.XX   |
| Parent(s)                   | N (% of total)       | N (% of total)       | p=0.XX   | N (% of total)       | N (% of total)       | p=0.XX   |
| Patient                     | N (% of total)       | N (% of total)       | p=0.XX   | N (% of total)       | N (% of total)       | p=0.XX   |
| Preoperative                |                      |                      |          |                     |                      |         |
| imaging, n (%)              |                      |                      |          |                     |                      |         |
| US                          | N (% of total)       | N (% of total)       | p=0.XX   | N (% of total)       | N (% of total)       | p=0.XX   |
| US+MRI                      | N (% of total)       | N (% of total)       | p=0.XX   | N (% of total)       | N (% of total)       | p=0.XX   |
| US+CT                       | N (% of total)       | N (% of total)       | p=0.XX   | N (% of total)       | N (% of total)       | p=0.XX   |
| Abscess on imaging, n (%)   |                      |                      |          |                     |                      |         |
| <3 cm                       | N (% of total)       | N (% of total)       | p=0.XX   | N (% of total)       | N (% of total)       | p=0.XX   |
| 3–6 cm                      | N (% of total)       | N (% of total)       | p=0.XX   | N (% of total)       | N (% of total)       | p=0.XX   |
| >6 cm                       | N (% of total)       | N (% of total)       | p=0.XX   | N (% of total)       | N (% of total)       | p=0.XX   |
| Multiple                    | N (% of total)       | N (% of total)       | p=0.XX   | N (% of total)       | N (% of total)       | p=0.XX   |
| Hospital, n (%)             |                     |                      |          |                     |                      |         |

Continued
implementation. Staff, representatives and stakeholders on patient, doctor and society level will be asked to participate in this implementation study. Structured interviews with healthcare professionals, patients, parents and other stakeholders will be held in order to identify the best implementation strategy, taking into account the impact of the results on current practice.

DISCUSSION
The CAPP study aims to identify the optimal treatment strategy for children presenting with complex appendicitis. Current points of debate that are investigated are the optimal surgical approach (laparotomy or laparoscopy) for children presenting with complex appendicitis without mass or abscess formation (subgroup 1); and the choice for direct appendectomy or initial non-operative treatment (consisting of intravenous antibiotics with or without (percutaneous) drainage procedure) for children presenting with complex appendicitis with mass and/or abscess (subgroup 2). At this moment these treatment strategies for paediatric complex appendicitis are all considered standard of care, which leads to significant heterogeneity in daily practice. Recent meta-analyses focusing on the treatment of complex appendicitis in children have confirmed that evidence is scarce, especially for patients that present with complex appendicitis with enlarged mass or abscess formation. Evidence for (the optimal treatment strategy in) children that present with complex appendicitis without mass or abscess is also relatively scarce. Only two small randomised clinical trials (RCTs) and some cohort studies (mostly historical cohorts) have been published focusing primarily on the overall complication rate of laparoscopic versus open appendectomy. These studies only detected small differences between these operative approaches. The heterogeneity in current daily practice reflects the lack of evidence and emphasises the need for well-designed studies.

### Choice of study design
The CAPP study is a nationwide prospective cohort study, that will collect prospective data of more than 1300 patients that are treated for complex appendicitis in more than 30 academic and (large) teaching hospitals in the Netherlands. Therefore, it will be a large prospective study investigating the treatment of both subgroups of complex appendicitis in children. Apart from the measurement of important outcome measures such as the proportion of complications, prospective data will be collected regarding life-impact outcomes (ie, quality of life and return to school), and cost-effectiveness of treatment strategies will be assessed. Furthermore, the study protocol has been designed by a multidisciplinary team, consisting of epidemiologists, paediatricians, infectiologists, gastroenterologists, (interventional) radiologists, patient support groups and (paediatric) surgeons. The nationwide and multidisciplinary character of this study is potentially beneficial for implementation and results will be generalisable to the entire Dutch population of children with complex appendicitis. Moreover, as nowadays global guidelines on the diagnostic work-up and treatment of acute appendicitis are followed by many countries, the management of patients is becoming increasingly comparable. Results of this study are therefore not only generalisable to the Dutch population, but to the international population as well.

 Ideally, the comparison between open and laparoscopic appendectomy for complex appendicitis without abscess and/or mass formation and between direct appendectomy and non-operative treatment for patients presenting with appendiceal abscess and/or mass would be investigated in an RCT. However, before the start of the CAPP study, we conducted a nationwide survey that pointed out that there was reluctance among (paediatric) surgeons to participate in an RCT comparing these different treatment strategies in the paediatric population. Reluctance was mostly based on a strong preference of surgeons for one of the treatment strategies. Therefore, we expected that an RCT design would not be feasible and decided...
### Table 4  Primary outcome subgroup 1

| Complications after 3 months, n (% of total) | Open appendectomy, n | Absolute difference in proportions | Unadjusted OR | Propensity score adjusted absolute difference | P value | Propensity score adjusted OR | P value |
|--------------------------------------------|----------------------|-----------------------------------|--------------|---------------------------------------------|---------|-------------------------------|---------|
| N (% of total) | N (% of total) | Absolute difference (95% CI) | OR (95% CI) | Absolute difference (95% CI) | p=0.XX | OR (95% CI) | p=0.XX |

Complication severity

| Clavien-Dindo I | N (% of total) | N (% of total) | Absolute Difference (95% CI) | OR (95% CI) | Absolute Difference (95% CI) | p=0.XX | OR (95% CI) | p=0.XX |
|-----------------|----------------|---------------|-----------------------------|------------|-----------------------------|---------|------------|---------|
| Clavien-Dindo II | N (% of total) | N (% of total) | Absolute Difference (95% CI) | OR (95% CI) | Absolute Difference (95% CI) | p=0.XX | OR (95% CI) | p=0.XX |
| Clavien-Dindo III | N (% of total) | N (% of total) | Absolute Difference (95% CI) | OR (95% CI) | Absolute Difference (95% CI) | p=0.XX | OR (95% CI) | p=0.XX |
| Clavien-Dindo IV | N (% of total) | N (% of total) | Absolute Difference (95% CI) | OR (95% CI) | Absolute Difference (95% CI) | p=0.XX | OR (95% CI) | p=0.XX |

*This column presents the pooled/combined results of the five propensity score strata.
†A similar table will be created for the subgroup analysis of patients with perioperative and histopathologically confirmed complex appendicitis without abscess or mass formation.

### Table 5  Primary outcome subgroup 2

| Complications after 3 months, n (% of total) | Direct appendectomy, n | Absolute difference in proportions | Unadjusted OR | Propensity score adjusted absolute difference | P value | Propensity score adjusted OR | P value |
|--------------------------------------------|------------------------|-----------------------------------|--------------|---------------------------------------------|---------|-------------------------------|---------|
| N (% of total) | N (% of total) | Absolute difference (95% CI) | OR (95% CI) | Absolute difference (95% CI) | p=0.XX | OR (95% CI) | p=0.XX |

Complication severity

| Clavien-Dindo I | N (% of total) | N (% of total) | Absolute Difference (95% CI) | OR (95% CI) | Absolute Difference (95% CI) | p=0.XX | OR (95% CI) | p=0.XX |
|-----------------|----------------|---------------|-----------------------------|------------|-----------------------------|---------|------------|---------|
| Clavien-Dindo II | N (% of total) | N (% of total) | Absolute Difference (95% CI) | OR (95% CI) | Absolute Difference (95% CI) | p=0.XX | OR (95% CI) | p=0.XX |
| Clavien-Dindo III | N (% of total) | N (% of total) | Absolute Difference (95% CI) | OR (95% CI) | Absolute Difference (95% CI) | p=0.XX | OR (95% CI) | p=0.XX |
| Clavien-Dindo IV | N (% of total) | N (% of total) | Absolute Difference (95% CI) | OR (95% CI) | Absolute Difference (95% CI) | p=0.XX | OR (95% CI) | p=0.XX |

*This column presents the pooled/combined results of the five propensity score strata.
†A similar table will be created for the subgroup analysis of patients with perioperative and histopathologically confirmed complex appendicitis with abscess and/or mass formation.
to perform a nationwide prospective cohort study. Although many clinicians and researchers still consider the RCT design as the gold standard for detecting causal effects, more practical designs such as patient preference and observational designs are increasingly used in large prospective studies. These study designs also have advantages, because they mimic practice, in which treatment decisions are made by the clinical team. Therefore results from the CAPP study reflect daily clinical practice, including preoperative decision making. Downside of our study design is that it potentially allows for confounding, as the choice of treatment may be affected by patient characteristics, patient/parent preferences, (interventional) radiologist’s skills, and surgeon’s preferences and skills. For example, the choice for non-operative treatment of children presenting with complex appendicitis with large abscess formation may depend on the presence of an interventional radiologist capable of performing a percutaneous drainage procedure. However, several steps were taken to reduce confounding in this study. Several confounders were identified by our multidisciplinary team before the start of the study and these variables will be taken into account in our propensity score analysis. To assess the influence of our choice of analyses, it was decided to perform a two-way propensity score analysis, including IPTW and stratification. In this way, we assess the influence of our methods for confounding adjustment on results. Moreover, sample size calculations showed that clinically significant differences in overall complications can be detected with our study design. Furthermore, with the introduction of standardised treatment strategies steps were taken to reduce heterogeneity in treatment between hospitals. All key points of these standardised treatment strategies are based on the recommendations of the Dutch national guideline. These measures will improve comparability of results of the participating hospitals.

**Table 6 Secondary outcomes subgroup 1**

|                      | Laparoscopic appendectomy, n | Open appendectomy, n | Unadjusted OR | Propensity score adjusted OR | P value |
|----------------------|-----------------------------|----------------------|---------------|------------------------------|---------|
| Any complication     |                             |                      |               |                              |         |
| Admission, n (%)     | N (% of total)              | N (% of total)       | OR (95% CI)   | OR (95% CI)                  | p=0.20  |
| 30 days, n (%)       | N (% of total)              | N (% of total)       | OR (95% CI)   | OR (95% CI)                  | p=0.20  |
| Intra-abdominal abscess (at 3 months), n (%) | N (% of total) | N (% of total) | OR (95% CI) | OR (95% CI) | p=0.20 |
| Secondary/prolonged bowel obstruction (at 3 months), n (%) | N (% of total) | N (% of total) | OR (95% CI) | OR (95% CI) | p=0.20 |
| Length of hospital stay (days) | Mean (SD) | Mean (SD) | Mean difference | Mean difference | p=0.20 |
| Level of pain (during admission) | Mean (SD) | Mean (SD) | Mean difference | Mean difference | p=0.20 |
| Extra visits to GP, outpatient clinic or ED | Mean (SD) | Mean (SD) | Mean difference | Mean difference | p=0.20 |
| NET QoL (PedQL 4.0) | Mean (SD) | Mean (SD) | Mean difference | Mean difference | p=0.20 |
| Admission | Mean (SD) | Mean (SD) | Mean difference | Mean difference | p=0.20 |
| 30 days | Mean (SD) | Mean (SD) | Mean difference | Mean difference | p=0.20 |
| 3 months | Mean (SD) | Mean (SD) | Mean difference | Mean difference | p=0.20 |
| Patient satisfaction (3 months) | Mean (SD) | Mean (SD) | Mean difference | Mean difference | p=0.20 |
| PSQ-18 | Mean (SD) | Mean (SD) | Mean difference | Mean difference | p=0.20 |
| Direct costs (3 months) | Mean (SD) | Mean (SD) | Mean difference | Mean difference | p=0.20 |
| Indirect costs (3 months) | Mean (SD) | Mean (SD) | Mean difference | Mean difference | p=0.20 |

*This column presents the pooled/combined results of the five propensity score strata.

ED, emergency department; GP, general practitioner; Hr-QoL, Health-related Quality of Life; NET, neuro-endocrine tumours; PSQ, Patient Satisfaction Questionnaire.

**Definition of complex appendicitis**

The CAPP study aims to investigate the complete process of care and outcomes for children with complex appendicitis, including the physician’s decision for one of the treatment strategies that are now considered usual care (ie, open or laparoscopic appendectomy, and non-operative treatment or direct appendectomy). To incorporate the preoperative decision-making process, all patients...
with a presumed diagnosis of complex appendicitis will be included in the study pre-operatively. Therefore, the inclusion and exclusion criteria are mostly based on the complex appendicitis prediction score that was previously developed by our research team. This scoring system combines clinical, biochemical and radiological variables in order to differentiate between simple and complex appendicitis. A cut-off point of four points is used for inclusion of patients in this study. Despite the diagnostic accuracy of 90%, inevitably some patients with simple appendicitis will be included in this study. Therefore we plan to perform an analysis on all included patients and an additional analysis that includes only patients with a diagnosis of complex appendicitis that is perioperatively and/or histopathologically confirmed. Classification of simple and complex appendicitis remains challenging, as no uniform definition for complex appendicitis is available yet. In the current literature various terms and definitions are used for appendiceal mass and complex appendicitis. Terms that are frequently used to describe the spectrum of complex appendicitis are signs of necrosis (black, blue or purple colour change), a visible hole in the appendix, an extraluminal fecolith, generalised peritonitis, and an appendiceal mass or abscess. Furthermore, ‘perforated appendicitis’, ‘complex appendicitis’ and ‘complicated’ appendicitis are terms that are used interchangeably. The same applies for the terms appendiceal ‘mass’ and ‘phlegmon’. Therefore in this study, it was decided to use an objective classification of perioperative and postoperative variables, that is, the classification suggested by Bhangu et al.

**Table 7** Secondary outcomes subgroup 2

| Non-operative treatment, n | Direct appendectomy, n | Unadjusted OR | Propensity score adjusted OR | P value |
|----------------------------|------------------------|---------------|-------------------------------|---------|
| Admission, n (%)           | N (% of total)         | N (% of total)| OR (95% CI)                   | p=0.22  |
| 30 days, n (%)             | N (% of total)         | N (% of total)| OR (95% CI)                   | p=0.22  |
| Intra-abdominal abscess (at 3 months), n (%) | N (% of total) | N (% of total) | OR (95% CI) | p=0.22 |
| Superficial site infection (at 3 months), n (%) | N (% of total) | N (% of total) | OR (95% CI) | p=0.22 |
| Secondary/prolonged bowel obstruction (at 3 months), n (%) | N (% of total) | N (% of total) | OR (95% CI) | p=0.22 |
| Length of hospital stay (days) | Mean (SD)              | Mean (SD)     | Mean difference               | p=0.22  |
| Level of pain (during admission) | Mean (SD)              | Mean (SD)     | Mean difference               | p=0.22  |
| Extra visits to GP, outpatient clinic or emergency department | Mean (SD)              | Mean (SD)     | Mean difference               | p=0.22  |
| No appendectomy after 3 months, n (%) | N (% of total)         | –             | –                             | –       |
| Recurrent appendicitis (3 months), n (%) | N (% of total)         | –             | –                             | –       |
| Early failure of non-operative treatment, n (%) | N (% of total)         | –             | –                             | –       |
| Interval appendectomy (at 3 months), n (%) | N (% of total)         | –             | –                             | –       |

**Hr-QoL (PedsQL 4.0)**

| Admission | Mean (SD) | Mean (SD) | Mean difference | Mean difference | p=0.22  |
| 30 days    | Mean (SD) | Mean (SD) | Mean difference | Mean difference | p=0.22  |
| 3 months   | Mean (SD) | Mean (SD) | Mean difference | Mean difference | p=0.22  |
| Patient satisfaction (3 months)                |                       |               |                  |         |
| NET Promoter Score | Mean (SD) | Mean (SD) | Mean difference | Mean difference | p=0.22  |
| PSQ-18     | Mean (SD) | Mean (SD) | Mean difference | Mean difference | p=0.22  |
| Direct costs (3 months) | Mean (SD) | Mean (SD) | Mean difference | Mean difference | p=0.22  |
| Indirect costs (3 months) | Mean (SD) | Mean (SD) | Mean difference | Mean difference | p=0.22  |

*This column presents the pooled/combined results of the five propensity score strata.

GP, general practitioner; Hr-QoL, Health-related Quality of Life; NET, neuro-endocrine tumours; PSQ, Patient Satisfaction Questionnaire.
Choice of primary outcome

Determining the primary outcome measure for studies comparing standard treatment strategies for complex appendicitis is challenging. Recently, an international consensus study led to the development of a core outcome set for clinical trials investigating any type of treatment of children with acute simple appendicitis. This core outcome set was developed in collaboration with several different stakeholders such as patients, parents, researchers and physicians. The complication rate appeared to be an important outcome that was mentioned by all stakeholders. Unfortunately, up till now, no core outcome set has been developed for studies investigating the optimal treatment strategy for children presenting with complex appendicitis. Therefore, the CAPP study minimally adheres to the outcomes as reported in the core outcome set for studies investigating the treatment of simple appendicitis. In line with this core outcome set, and based on previous qualitative studies investigating possible promoting and obstructing factors for implementation, we decided to choose the proportion of patients experiencing complications within 3 months after the start of treatment as primary outcome. In addition, we think that the overall complication rate is the most relevant outcome that can persuade doctors (and patients) to choose between the treatment strategies.

Previous studies have shown that the differences in complication rate between the treatment strategies that are investigated in this study might be relatively small. Therefore, it could be possible that no difference in complication rate will be found in this large prospective cohort study. If no clinically relevant difference is found in the primary outcome, the difference in secondary outcomes, such as HR-QoL and cost-effectiveness, may become more important. Secondary outcomes of this study were also chosen to reflect the same five core areas as the core outcome set for children with simple appendicitis, that is, death, physiological/clinical manifestations, life impact, resource use and adverse events. Besides, our primary outcome (overall complication rate), life impact outcomes (ie, paediatric quality of life, return to school or normal activities) and resource use outcomes (ie, hospital readmission, need for reoperation, need for appendectomy after initial non-operative treatment) are taken into account. High-quality data on these secondary outcomes can furthermore be used by the treating physician to inform patients on the advantages and disadvantages of the treatment options, which will facilitate shared decision making.

Length of follow-up

The majority of complications after appendectomy occur within 3 months after the start of treatment. Although long-term complications (>30 days after appendectomy), such as adhesive small bowel obstruction and incisional hernia, do occur after appendectomy in children, their prevalence is reported to be less than 1%. Furthermore, as appendicitis is an acute disease it is expected to affect HR-QoL and medical costs for only a short period of time. As it is expected that the majority of children is recovered within 3 months, a follow-up duration of 3 months was chosen for this study. However, all patients treated in this prospective cohort study will be asked for their consent to approach them to participate in future studies in which their long-term outcomes (more than 3 months) will be investigated. Information regarding the long-term results of non-operative treatment and the necessity of interval appendectomy is scarce in children. One randomised controlled trial has been published recently in which children treated non-operatively for appendix mass were randomised between active observation or planned interval appendectomy. This study showed a rate of 6% severe complications after interval appendectomy, whereas only 12% of children under active observation developed recurrent appendicitis within 1 year follow-up. Therefore, interval appendectomy was not incorporated as a routine procedure after non-operative treatment in the CAPP study.

Long-term follow-up would be of additional interest for those patients that present with a faecolith. Previous studies investigating non-operative treatment in both patients with simple appendicitis and complex appendicitis, have reported that a faecolith might increase the risk of recurrent appendicitis. As the CAPP study only has a follow-up period of 3 months, important information regarding recurrent appendicitis in the group of patients that is treated non-operatively would be missed. Therefore, all patients that are treated in this study will be asked to participate in long-term follow-up.

This nationwide prospective cohort study will be the first study that provides high-quality evidence regarding the optimal treatment strategy for complex appendicitis in children. Results of this study will be used to support recommendations for (inter)national guidelines regarding the treatment of acute appendicitis, which will improve shared decision making and ultimately lead to uniform optimal treatment of complex appendicitis in the paediatric population.

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REFERENCES

1. Addiss DG, Shaffer N, Fowler BS, et al. The epidemiology of appendicitis and appendectomy in the United States. Am J Epidemiol 1990;132:910–25.
2. Anderson JE, Bickler SW, Chang DC, et al. Examining a common disease with unknown etiology: trends in epidemiology and surgical management of appendicitis in California, 1995-2009. World J Surg 2012;36:278-84.
3. van Rossem CC, Bolimers MDM, Schirenmaker MPH, et al. Prospective nationwide outcome audit of surgery for suspected acute appendicitis. Br J Surg 2016;103:144–51.
4. Anderson RE. The natural history and traditional management of appendicitis revisited: spontaneous resolution and predominance of prehospital perforations imply that a correct diagnosis is more important than an early diagnosis. World J Surg 2007;31:86–92.
5. Cobben LP, de Van Otterloo AM, Puylaert JB. Spontaneously resolving appendicitis: frequency and natural history in 60 patients. Radiology 2004;232:173-80.
6. Ruber M, Andersson M, Pettersson BF, et al. Systemic Th17-lymphocyte pattern in gangrenous appendicitis but not in phlegmonous appendicitis. Surgery 2010;147:366–72.
7. Di Saverio S, Podda M, De Simone B, et al. Diagnosis and treatment of acute appendicitis: 2020 update of the WSES Jerusalem guidelines. World J Emerg Surg 2020;15:27.
8. Gorter RR, Eker HH, Gorter-Stam MAW, et al. Diagnosis and management of acute appendicitis. EAES consensus development conference 2015. Surg Endosc 2016;30:4668–90.
9. Bolimmers MD, van Rossem CC, Gorter RR, et al. Imaging in pediatric appendicitis is key to a low normal appendix percentage: a national audit on the outcome of appendectomy for appendicitis in children. Pediatr Surg Int 2018;34:543–51.
10. Markar SR, Blackburn S, Cobb R, et al. Laparoscopic versus open appendectomy for complicated and uncomplicated appendicitis in children. J Gastrointest Surg 2012;16:1993–2004.

16 van Amstel P, et al. BMJ Open 2022;12:e054826. doi:10.1136/bmjopen-2021-054826

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11. Cheng Y, Xiong X, Lu J, et al. Early versus delayed appendicectomy for appendiceal phlegmon or abscess. *Cochrane Database Syst Rev* 2017;6:CD011670.

12. Similcic I, Symeonides P, Shorthouse AJ, et al. A meta-analysis comparing conservative treatment versus acute appendectomy for complicated appendicitis (abscess or phlegmon). *Surgery* 2010;147:818–29.

13. Bom WJ, Knaapen M, Gorter RR. Revised guideline for acute appendicitis. *Amendments to diagnostics and treatment*. Ned Tijdschr Geneeskd 2020;164 https://pubmed.ncbi.nlm.nih.gov/32406636/.

14. Knaapen M, Hall NJ, van der Lee JH, et al. Establishing a core outcome set for treatment of uncomplicated appendicitis in children: study protocol for an international Delphi survey. *BMJ Open* 2019;9:e028881.

15. Gorter RR, van den Boom AL, Heij HA, et al. A scoring system to predict the severity of appendicitis in children. *J Surg Res* 2016;200:452–9.

16. Dindo D, Demartines N, Clavien P-A. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004;240:205–13.

17. Berrios-Torres SI, Umscheid CA, Bratzler DW, et al. Centers for disease control and prevention guideline for the prevention of surgical site infection, 2017. *JAMA Surg* 2017;152:784–91.

18. Varni JW, Seid M, Rode CA. The PedsQL: measurement model for the pediatric quality of life inventory. *Med Care* 1999;37:126–39.

19. Wille N, Badia X, Bonsel G, et al. The EQ-5D-Y: definition for perforated appendicitis derived from a prospective randomized trial. *J Pediatr Surg* 2014;49:1893–7.

20. Foulad D, Kaufman JD, Chandler NM. Pathology findings following interval appendectomy: should it stay or go? *J Pediatr Surg* 2020;55:737–41.

21. Bouwmans C, Hakkaart-van Roijen L, Koopmanschap M. *Handboek IMTA medical cost questionnaire (iMCQ)*. Rotterdam: IMTA, Erasmus University Rotterdam, 2013.

22. Bouwmans C, Krol M, Severens L, et al. The IMTA productivity cost questionnaire: a standardized instrument for measuring and Valuing health-related productivity losses. *Value Health* 2015;18:753–8.

23. Bhanu A, Sereide K, Di Saverio S, et al. Acute appendicitis: modern understanding of pathogenesis, diagnosis, and management. *The Lancet* 2015;386:1278–87.

24. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika* 1983;70:41–55.

25. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behav Res* 2011;46:399–424.

26. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. *Stat Med* 2015;34:3661–79.

27. Castor EDC. Castor electronic data capture, 2019. Available: https://castoredc.com [Accessed 28 Aug 2019].