BMJ Open

The identification of the optimal treatment strategy for complex appendicitis in the pediatric population; a protocol for a multicenter prospective cohort study (CAPP study)

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-054826
Article Type:	Protocol
Date Submitted by the Author:	24-Jun-2021
Complete List of Authors:	van Amstel, Paul; Emma Children's Hospital, Amsterdam UMC, University of Amsterdam & Vrije Universiteit Amsterdam, Department of Pediatric Surgery; Amsterdam UMC Location AMC Bakx, Roel; Emma Children's Hospital, Amsterdam UMC, University of Amsterdam & Vrije Universiteit Amsterdam, Department of Pediatric Surgery; Amsterdam UMC Location AMC van der Lee, Johanna H.; Amsterdam UMC, University of Amsterdam & Vrije Universiteit Amsterdam, Pediatric Clinical Research Office; Knowledge Institute of the Dutch Association of Medical Specialists van der Weide, Marijke C.; Amsterdam UMC, University of Amsterdam & Vrije Universiteit Amsterdam, Obstetrics and Gynaecology Eekelen, Rik; Amsterdam UMC Location AMC, Centre for Reproductive Medicine Derikx, Joep; Emma Children's Hospital, Amsterdam UMC, University of Amsterdam & Vrije Universiteit Amsterdam, Department of Pediatric Surgery; Amsterdam UMC Location AMC van Heurn, Ernest; Emma Children's Hospital, Amsterdam UMC, University of Amsterdam & Vrije Universiteit Amsterdam, Department of Pediatric Surgery; Amsterdam UMC Location AMC Gorter, Ramon R.; Emma Children's Hospital, Amsterdam UMC, University of Amsterdam & Vrije Universiteit Amsterdam, Department of Pediatric Surgery; Amsterdam UMC Location AMC
Keywords:	PAEDIATRIC SURGERY, Paediatric colorectal surgery < PAEDIATRIC SURGERY, Paediatric gastroenterology < PAEDIATRICS

The identification of the optimal treatment strategy for complex appendicitis in the pediatric population; a protocol for a multicenter prospective cohort study (CAPP study)

Paul van Amstel[1], MD, Roel Bakx[1] MD PhD, Johanna H van der Lee[2], MD PhD, Marijke C van der Weide[3], MD PhD, Rik van Eekelen[4], MD PhD, Joep PM Derikx[1], MD PhD, LW Ernest van Heurn[1], MD PhD, Ramon R. Gorter[1], MD PhD, on behalf of the CAPP collaborative study group.

1. Emma Children's Hospital, Amsterdam UMC, University of Amsterdam & Vrije Universiteit Amsterdam, Department of Pediatric Surgery, Amsterdam, The Netherlands.
2. Amsterdam UMC, University of Amsterdam & Vrije Universiteit Amsterdam, Pediatric Clinical Research Office, Amsterdam, and Knowledge Institute of the Dutch Association of Medical Specialists, Utrecht, the Netherlands.
3. Amsterdam UMC, University of Amsterdam & Vrije Universiteit Amsterdam, Department of Obstetrics and Gynaecology, Amsterdam, the Netherlands.
4. Amsterdam UMC, location Academic Medical Centre, Centre for Reproductive Medicine, Amsterdam, the Netherlands.

Correspondence:

Name: P. van Amstel
Address: Emma Children's Hospital, Amsterdam UMC, University of Amsterdam & Vrije Universiteit Amsterdam, Department of Pediatric Surgery, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands.
Email: p.vanamstel@amsterdamumc.nl
Telephone: +31 20 56 65693
Fax: +31 20 444 2135

Abstract

Introduction: In daily practice large heterogeneity in the treatment of children with complex appendicitis exists. Complex appendicitis can be divided in 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-center, comparative, non-randomized 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 to laparoscopic appendectomy for children without appendiceal mass and/or abscess and initial non-operative treatment (i.e. 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 two years and nine months, a sample size of 1308 patients is aimed. Primary outcome is the proportion of patients experiencing any complication at three 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 (inter)national conferences.

Trial registration number: NCT04755179; NL9371

Strengths and limitations of this study

- Generalizable data gathered from a large cohort of children treated for acute complex appendicitis according to standardized treatment strategies in more than 30 academic and (large) teaching hospitals in the Netherlands.
- Study protocol designed by a multidisciplinary team consisting of epidemiologists, pediatricians, infectiologists, gastro-enterologists, (interventional) radiologists, patient support groups and (pediatric) 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-randomized study design potentially allows for confounding by indication.

Introduction

Acute appendicitis is one of the most common gastro-intestinal disorders with a lifetime incidence of 7-9%.[1 2] 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.[3] Insights in the pathogenesis of appendicitis have led to the recognition of two distinct types: simple (or uncomplicated) and complex (or complicated) appendicitis.[4-6] 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.[3] 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.[7 8] In recent times laparoscopic appendectomy is increasingly applied in both adults (80%) and children (60%).[3 9] Potential benefits reported for this approach (compared to 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, level of evidence on this topic is low and inconsistency in results is found between studies.[10]

Evidence regarding the treatment of children presenting with complex appendicitis with mass and/or abscess formation is scarce as well. Some surgeons favor 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 randomized 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.[11] 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 to direct appendectomy.[12] 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.[13]

The lack of high-quality data regarding the management of complex appendicitis in the pediatric population emphasizes the need for well-designed studies in order to identify the optimal treatment strategy for complex appendicitis in the pediatric population. The aim of this study is twofold; firstly, to evaluate the outcomes (in terms of complications, health-related Quality of Life, and costs) of open appendectomy compared to laparoscopic appendectomy for children with a complex appendicitis without appendiceal mass and/or abscess. Secondly to compare the outcomes (in terms of complications, health-related Quality of Life, and costs) of initial non-operative treatment (i.e. 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 at the 29th of January 2021 (NCT04755179) and the Netherlands Trial Register at the 4th of April 2021 (NL9371).

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-center, comparative, non-randomized prospective cohort study with standardized treatment strategies. The choice of treatment is jointly decided by the physician and the patient/parents, and subsequently a standardized treatment strategy is followed. Data are collected during admission, at one and three 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.[14]

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 upon imaging confirmed acute appendicitis and the following predefined criteria (regarding the severity of appendicitis):

- Four points or more on the complex appendicitis prediction score.[15]

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.

Exclusion criteria:

- Adult patients (≥18 years old)
- Patients with a preoperative suspicion of simple appendicitis, based on less than four points on the complex appendicitis prediction score.[15]

Complex appendicitis prediction score

The complex appendicitis prediction score is a pediatric scoring system that predicts the probability of complex appendicitis.[15] This scoring system with a scale ranging from 0 to 10, consists of five preoperative variables (each awarded points): diffuse abdominal guarding (three points), CRP level >38 mg/L (two points), signs of complex appendicitis on ultrasound (two points), temperature >37.5°C (one point), and more than one day of abdominal pain (two points). In an independent validation in a pediatric cohort, this scoring system had a

diagnostic accuracy of 91% (95%CI: 84-98%), 90% (95%CI: 54-99%) sensitivity, 91% (95%CI: 79-97%) specificity, positive likelihood ratio of 10 (95%CI: 4.19-23.42) and negative likelihood ratio of 0.11 (95%CI: 0.02-0.71).[15]

Subgroups of complex appendicitis

Patients will be classified into the two subgroups of complex appendicitis based upon 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 categorized as subgroup 1 (complex appendicitis without abscess or mass). If signs suggestive of intra-abdominal abscess and/or enlarged mass are present, patients will be categorized as subgroup 2 (complex appendicitis with abscess or mass). 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 at the 12th of 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 two years and nine 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%.[3 9] 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.[13]

Sample size calculation

Based upon 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.

Standardized treatment strategies

Standardized treatment protocols were developed in order to reduce the heterogeneity in treatment between the participating hospitals. All participating sites agreed to conform to these standardized treatment protocols to the best of their ability. These standardized treatments follow the recommendations given in the Dutch national guideline regarding the pre-, peri- and postoperative care. See Appendix 1 and Box 1 for a detailed description of the treatment strategies.

Study outcomes

Primary outcome

The primary outcome is defined as the proportion of patients experiencing any complication within three 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 categorize 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 gastro-intestinal decompression with a nasogastric tube.
- Anesthesia related complications, such as pneumonia
- Incisional hernia: Any abdominal wall gap with or without a bulge in the area of a postoperative scar 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 three 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 three months after inclusion
- Proportion of patients with a superficial site infection within three months after inclusion
- Proportion of patients with a secondary/prolonged bowel obstruction within three months after inclusion
- Proportion of patients not having to undergo appendectomy within three months after inclusion
- Proportion of patients experiencing recurrent appendicitis within three 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 three months after inclusion (histopathologically no sign of recurrent appendicitis)

Patient-related endpoints:

- Level of pain: assessed by the Numeric Rating Scale (NRS) and total use of pain medication during admission
- Health-related Quality of Life 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 three 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 three 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 three 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, will be included in a secondary analysis.[23]

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 (Figure 3 and Figure 4). Identified variables for subgroup 1 are age, 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 pre-operatively using standardized 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 linearized propensity score will be compared between treatment groups. Balancing will be assessed by comparing the standardized 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 standardized 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 1 and 2. Data will be presented using absolute numbers and percentages for discrete outcomes. Continuous outcomes will be presented as means with standard deviation or medians with interquartile ranges, according to their distribution. Baseline characteristics will be compared between treatment groups and presented for both the pre-matching cohort and

post-matching cohort. For each subgroup of complex appendicitis a baseline characteristics table will be created.

Primary endpoint analysis

Proportion of complications after three 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 3 and 4.

Unadjusted and propensity score adjusted differences in proportions and odds ratios (OR) will be presented with their 95% confidence intervals.

Secondary endpoints analysis

Data on the secondary outcomes will be presented as displayed in tables 5 and 6.

Unadjusted and propensity score adjusted odds ratios 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, one month, and three months. In this way both the child's and parents' perspective will be assessed. No difference in effect is anticipated after three months, as acute appendicitis is an acute disease with a relatively short period of disutility.

Costs will be assessed from the societal perspective, integrating health care 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, one month, and three 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 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 €20,000 / QALY. QALY's will be calculated using the EQ 5D youth and EQ-5D-Proxy questionnaires. As acute appendicitis is an acute disease, disutility might be short term in our study. Therefore, QALY's will be transformed to quality-adjusted life months (QALMs).

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 five 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 (i.e. healthcare professionals, patients and parents, and insurance companies).

Cost analysis

Identification of all health care related costs will be recorded per patient. Potential determinants influencing the budget impact analysis 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 spread sheet will be used in which obtained data is inserted. At completion of this study, based upon 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 health care budget per annum for the Netherlands in terms of cost reduction.

Ethics 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 is handled confidentially in accordance with the General Data Protection Regulation. Castor Electronic Data Capture will be used for data collection and storage.[27] 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 onsite monitoring of participating sites by an independent and qualified monitor.

Ethics

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 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 pediatric 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 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 pediatric 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.[10 12 28] Evidence for (the optimal treatment strategy in) children that present with complex appendicitis without mass or abscess is also relatively scarce. Only two small 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.[10 29 30] The heterogeneity in current daily practice reflects the lack of evidence and emphasizes the need for well-designed studies.

Choice of study design

The CAPP study is a nation-wide 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 (i.e. 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, pediatricians, infectiologists, gastro-enterologists, (interventional) radiologists, patient support groups and (pediatric) surgeons. The nationwide and multidisciplinary character of this study is potentially beneficial for implementation and results will be generalizable to the entire Dutch population of children with complex appendicitis.

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 a Randomized Clinical Trial (RCT). However, before the start of the CAPP study, we conducted a nationwide survey that pointed out that there was reluctance amongst (pediatric) surgeons to participate in an RCT comparing these different treatment strategies in the pediatric 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 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.[31] 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 pre-operative 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. Standardized treatment strategies were introduced to improve comparability between hospitals. Additionally, 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.

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 (i.e. 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 in- 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.[15] 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, generalized peritonitis, and an appendiceal mass or abscess.[23 32 33] 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 peri- and postoperative variables, i.e. the classification suggested by Bhangu et al.[23]

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.[14] 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 upon previous qualitative studies investigating possible promoting and obstructing factors for implementation, we decided to choose the proportion of patients experiencing complications within three months after the start of treatment as primary outcome. In addition, we think that 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 health-related quality of life 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, i.e. death, physiological/clinical manifestations, life impact, resource use and adverse events. Besides our primary outcome (overall complication rate), life impact outcomes (i.e. pediatric quality of life, return to school or normal activities) and resource use outcomes (i.e. 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 three 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%.[34] Furthermore, as appendicitis is an acute disease it is expected to affect health-related quality of life and medical costs for only a short period of time. As it is expected that the majority of children is recovered within three months, a follow-up duration of three 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 three 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 randomized controlled trial has been published recently in which children treated non-operatively for appendix mass were randomized between active observation or planned interval appendectomy.[35] This study showed a rate of 6% severe complications after interval appendectomy, whereas only 12% of children under active observation developed recurrent appendicitis within one year follow-up. Therefore, interval appendectomy was not incorporated as a routine procedure after non-operative treatment in the CAPP study. Opponents of this strategy point to the possibility of missing neuro-endocrine tumors (NETs) of the appendix. However, several studies have shown that NETs are rarely found at histopathological examination (0-0.4%).[36-39]

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.[40-42] As the CAPP study only has a follow-up period of three 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 pediatric population.

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(5):910-25. doi: 10.1093/oxfordjournals.aje.a115734 [published Online First: 1990/11/01]
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(12):2787-94. doi: 10.1007/s00268-012-1749-z [published Online First: 2012/09/06]
3. van Rossem CC, Bolmers MD, Schreinemacher MH, et al. Prospective nationwide outcome audit of surgery for suspected acute appendicitis. *Br J Surg* 2016;103(1):144-51. doi: 10.1002/bjs.9964 [published Online First: 2015/10/29]
4. Andersson 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(1):86-92. doi: 10.1007/s00268-006-0056-y [published Online First: 2006/12/21]
5. Cobben LP, de Van Otterloo AM, Puylaert JB. Spontaneously resolving appendicitis: frequency and natural history in 60 patients. *Radiology* 2000;215(2):349-52. doi: 10.1148/radiology.215.2.r00ma08349 [published Online First: 2000/05/05]
6. Ruber M, Andersson M, Petersson BF, et al. Systemic Th17-like cytokine pattern in gangrenous appendicitis but not in phlegmonous appendicitis. *Surgery* 2010;147(3):366-72. doi: 10.1016/j.surg.2009.09.039 [published Online First: 2009/11/07]
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(1):27. doi: 10.1186/s13017-020-00306-3 [published Online First: 2020/04/17]
8. Gorter RR, Eker HH, Gorter-Stam MA, et al. Diagnosis and management of acute appendicitis. EAES consensus development conference 2015. *Surg Endosc* 2016;30(11):4668-90. doi: 10.1007/s00464-016-5245-7 [published Online First: 2016/10/28]
9. Bolmers 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(5):543-51. doi: 10.1007/s00383-018-4244-2 [published Online First: 2018/03/11]
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(10):1993-2004. doi: 10.1007/s11605-012-1962-y [published Online First: 2012/07/20]
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. doi: 10.1002/14651858.CD011670.pub2 [published Online First: 2017/06/03]
12. Simillis C, Symeonides P, Shorthouse AJ, et al. A meta-analysis comparing conservative treatment versus acute appendectomy for complicated appendicitis (abscess or phlegmon). *Surgery* 2010;147(6):818-29. doi: 10.1016/j.surg.2009.11.013 [published Online First: 2010/02/13]
13. Bom WJ, Knaapen M, Gorter RR, et al. [Revised guideline for acute appendicitis. Amendments to diagnostics and treatment]. *Ned Tijdschr Geneeskd* 2020;164 [published Online First: 2020/05/15]
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(5):e028861. doi: 10.1136/bmjopen-2018-028861 [published Online First: 2019/05/28]
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(2):452-9. doi: 10.1016/j.jss.2015.08.042 [published Online First: 2015/10/06]

16. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004;240(2):205-13. doi: 10.1097/01.sla.0000133083.54934.ae [published Online First: 2004/07/27]
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(8):784-91. doi: 10.1001/jamasurg.2017.0904 [published Online First: 2017/05/04]
18. Varni JW, Seid M, Rode CA. The PedsQL™: Measurement Model for the Pediatric Quality of Life Inventory. *Medical Care* 1999;37(2):126-39.
19. Wille N, Badia X, Bonsel G, et al. Development of the EQ-5D-Y: a child-friendly version of the EQ-5D. *Qual Life Res* 2010;19(6):875-86. doi: 10.1007/s11136-010-9648-y [published Online First: 2010/04/21]
20. Thayaparan AJ, Mahdi E. The Patient Satisfaction Questionnaire Short Form (PSQ-18) as an adaptable, reliable, and validated tool for use in various settings. *Med Educ Online* 2013;18:21747. doi: 10.3402/meo.v18i0.21747 [published Online First: 2013/07/26]
21. Bouwmans C, Hakkaart-van Roijen L, Koopmanschap M, et al. Handleiding iMTA medical cost questionnaire (iMCQ). *Rotterdam: iMTA, Erasmus Universiteit Rotterdam* 2013
22. Bouwmans C, Krol M, Severens H, et al. The iMTA Productivity Cost Questionnaire: A Standardized Instrument for Measuring and Valuing Health-Related Productivity Losses. *Value Health* 2015;18(6):753-8. doi: 10.1016/j.jval.2015.05.009 [published Online First: 2015/09/28]
23. Bhangu A, Søreide K, Di Saverio S, et al. Acute appendicitis: modern understanding of pathogenesis, diagnosis, and management. *The Lancet* 2015;386(10000):1278-87. doi: 10.1016/s0140-6736(15)00275-5
24. PR R, DB R. The central role of the propensity score in observational studies for causal effects. *Biometrika* 1983;70(1):41-55.
25. Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. *Multivariate Behavioral Research* 2011;46(3):399-424. doi: 10.1080/00273171.2011.568786
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(28):3661-79. doi: 10.1002/sim.6607 [published Online First: 2015/08/05]
27. Castor EDC. Castor Electronic Data Capture 2019 [27 Aug. 2019]. Available from: https://castoredc.com accessed August 28, 2019.
28. van Amstel P, Sluckin TC, van Amstel T, et al. Management of appendiceal mass and abscess in children; early appendectomy or initial non-operative treatment? A systematic review and meta-analysis. *Surg Endosc* 2020;34(12):5234-49. doi: 10.1007/s00464-020-07822-y [published Online First: 2020/07/28]
29. Lintula H, Kokki H, Vanamo K, et al. Laparoscopy in children with complicated appendicitis. *J Pediatr Surg* 2002;37(9):1317-20. doi: 10.1053/jpsu.2002.34998 [published Online First: 2002/08/24]
30. Oka T, Kurkchubasche AG, Bussey JG, et al. Open and laparoscopic appendectomy are equally safe and acceptable in children. *Surg Endosc* 2004;18(2):242-5. doi: 10.1007/s00464-003-8140-y [published Online First: 2003/12/24]
31. Minneci PC, Hade EM, Lawrence AE, et al. Association of Nonoperative Management Using Antibiotic Therapy vs Laparoscopic Appendectomy With Treatment Success and Disability Days in Children With Uncomplicated Appendicitis. *Jama* 2020;324(6):581-93. doi: 10.1001/jama.2020.10888 [published Online First: 2020/07/31]
32. Blakely ML, Williams R, Dassinger MS, et al. Early vs interval appendectomy for children with perforated appendicitis. *Arch Surg* 2011;146(6):660-5. doi: 10.1001/archsurg.2011.6 [published Online First: 2011/02/23]

33. St Peter SD, Sharp SW, Holcomb GW, 3rd, et al. An evidence-based definition for perforated appendicitis derived from a prospective randomized trial. *J Pediatr Surg* 2008;43(12):2242-5. doi: 10.1016/j.jpedsurg.2008.08.051 [published Online First: 2008/12/02]
34. Rasmussen T, Fonnes S, Rosenberg J. Long-Term Complications of Appendectomy: A Systematic Review. *Scand J Surg* 2018;107(3):189-96. doi: 10.1177/1457496918772379 [published Online First: 2018/05/17]
35. Hall NJ, Eaton S, Stanton MP, et al. Active observation versus interval appendicectomy after successful non-operative treatment of an appendix mass in children (CHINA study): an open-label, randomised controlled trial. *The Lancet Gastroenterology & Hepatology* 2017;2(4):253-60. doi: 10.1016/s2468-1253(16)30243-6
36. Fouad D, Kauffman JD, Chandler NM. Pathology findings following interval appendectomy: Should it stay or go? *J Pediatr Surg* 2020;55(4):737-41. doi: 10.1016/j.jpedsurg.2019.05.001 [published Online First: 2019/05/28]
37. Gorter RR, van Amstel P, van der Lee JH, et al. Unexpected findings after surgery for suspected appendicitis rarely change treatment in pediatric patients; Results from a cohort study. *J Pediatr Surg* 2017;52(8):1269-72. doi: 10.1016/j.jpedsurg.2017.02.012 [published Online First: 2017/03/18]
38. Kim SS, Kays DW, Larson SD, et al. Appendiceal carcinoids in children--management and outcomes. *J Surg Res* 2014;192(2):250-3. doi: 10.1016/j.jss.2014.06.031 [published Online First: 2014/07/21]
39. Otake S, Suzuki N, Takahashi A, et al. Histological analysis of appendices removed during interval appendectomy after conservative management of pediatric patients with acute appendicitis with an inflammatory mass or abscess. *Surg Today* 2014;44(8):1400-5. doi: 10.1007/s00595-014-0950-0 [published Online First: 2014/06/17]
40. Ein SH, Langer JC, Daneman A. Nonoperative management of pediatric ruptured appendix with inflammatory mass or abscess: presence of an appendicolith predicts recurrent appendicitis. *J Pediatr Surg* 2005;40(10):1612-5. doi: 10.1016/j.jpedsurg.2005.06.001 [published Online First: 2005/10/18]
41. Mahida JB, Lodwick DL, Nacion KM, et al. High failure rate of nonoperative management of acute appendicitis with an appendicolith in children. *J Pediatr Surg* 2016;51(6):908-11. doi: 10.1016/j.jpedsurg.2016.02.056 [published Online First: 2016/03/29]
42. Tanaka Y, Uchida H, Kawashima H, et al. Long-term outcomes of operative versus nonoperative treatment for uncomplicated appendicitis. *J Pediatr Surg* 2015;50(11):1893-7. doi: 10.1016/j.jpedsurg.2015.07.008 [published Online First: 2015/08/12]

Collaborators: The CAPP collaborative study group includes the following contributors: H.A. Rippen[5], J. Berkhof[6], B.G.P. Koot[7], M. van der Kuip[8], R.R. van Rijn[9], H.J. Bonjer[10], J. Jansen[11], M.A. Lijkwan[12], G.D. Musters[12], P. Boele van Hensbroek[13], M. Springer[13], F.C. van Eijck[14], M.D.P. Luyer[15], A. Jairam[15], L.M. de Widt[16], M. Knaapen[16], C.M.G. Keyzer-Dekker[17], R.M.H. Wijnen[17], G.M.P. Diepenhorst[18], K.M.A. Dreuning[18], M.M. Poelman[19], D. Verver[19], P. van Duijvendijk[20], M.E. van der Sande[20], J.W.A. Oosterhuis[21], G.W. Zijp[22], E.H. Pasveer[22], R.P.R. Groenendijk[23], J.L.A. van Vugt[23], W.J. Vles[24], C.A. Selles[24], V.B. Nieuwenhuijs[25], J.T. Hoffman[25], J.W.A. Leijtens[26], E.G.M. Vosbeek[26], C.C. van Rossem[27], M.P. Gaspersz[27], M.H.M. Bender[28], B.J. Corten[28], E.C.J. Consten[29 30], M.F.J. Seesing[29], T.S. Bijlsma[31], S.M.L. The[31], L.E. Janssen[31], V.J. Leijdekkers[32], M.V. Nijenhuis[32], S.M.B.I. Botden[33], M. Joosten[33], A.L.A. Bloemendaal[34], C.F.J.M. Blanken-Peeters[35], W.M. IJgosse[35], A. Meij-de Vries[36], M.M. Bruntink[36], P.M.N.Y.H. Go[37], M. Pool[37], S.J. Oosterling[38], T.C. Derksen[38], A.A.W. van Geloven[39], T.T. Poels[39], J.B.F. Hulscher[40], F.C. den Boer[41], S.F. Hardon[41], F.P. Garssen[42], T. Wagner[42], M.F. Lutke Holzik[43], M.B.G.M. Decaestecker[43], E.G. Boerma[44], D. Schweitzer[44]. The surgical, pediatric, radiology, and emergency departments of the following hospitals contribute to the execution of this study: Amsterdam University Medical Centers, Amsterdam, the Netherlands; Admiraal de Ruyter Hospital, Goes, the Netherlands; Albert Schweitzer Hospital, Dordrecht, the Netherlands; Amphia, Breda, the Netherlands; Bravis Hospital, Bergen op Zoom, the Netherlands; Catharina Hospital, Eindhoven, the Netherlands; Dijklander Hospital, Hoorn, the Netherlands; Erasmus Medical Center, Rotterdam, the Netherlands; Flevo Hospital, Almere, the Netherlands; Franciscus Gasthuis & Vlietland, Rotterdam, the Netherlands; Gelre Hospitals, Apeldoorn/Zutphen, the Netherlands; Haaglanden Medical Center, The Hague, the Netherlands; Haga Hospital, The Hague, the Netherlands; IJsselland Hospital, Capelle aan den IJssel, the Netherlands; Ikazia Hospital, Rotterdam, the Netherlands; Isala, Zwolle, the Netherlands; Laurentius Hospital, Roermond, the Netherlands; Maasstad Hospital, Rotterdam, the Netherlands; Maxima Medical Center, Veldhoven, The Netherlands; Meander Medical Center, Amersfoort, the Netherlands; Noordwest Ziekenhuisgroep, Alkmaar, the Netherlands; OLVG, Amsterdam the Netherlands; Radboudumc, Nijmegen, the Netherlands; Reinier de Graaf Gasthuis, Delft, the Netherlands; Rijnstate, Arnhem, the Netherlands; Red Cross Hospital, Beverwijk, the Netherlands; St. Antonius Hospital, Nieuwegein, the Netherlands; Spaarne Gasthuis, Haarlem, the Netherlands; Tergooi, Hilversum, the Netherlands; University Medical Center Groningen, Groningen, the Netherlands; Zaans Medical Center, Zaandam, the Netherlands;

Amstelland Hospital, Amstelveen, the Netherlands; Ziekenhuisgroep Twente, Almelo, the Netherlands; Zuyderland Medical Center, Heerlen/Sittard, the Netherlands.

Affiliations:

[5]Dutch Child and Hospital Foundation, Utrecht, the Netherlands. [6]Department of Epidemiology and Biostatistics, VU University Medical Center, Amsterdam, the Netherlands. [7]Department of Pediatric Gastroenterology, Emma Children's Hospital, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands. [8]Department of Pediatric Infectious Diseases and Immunology, Emma Children's Hospital, Amsterdam UMC, Amsterdam, the Netherlands. [9]Department of Radiology and Nuclear Medicine, Emma Children's Hospital, University of Amsterdam, Amsterdam, the Netherlands. [10]Department of Surgery, Amsterdam UMC, University of Amsterdam & Vrije Universiteit Amsterdam, Amsterdam, the Netherlands. [11]Department of Surgery, Admiraal de Ruyter Hospital, Goes, the Netherlands. [12]Department of Surgery, Albert Schweitzer Hospital, Dordrecht, the Netherlands. [13]Department of Surgery, Amphia, Breda, the Netherlands. [14]Department of Surgery, Bravis Hospital, Bergen op Zoom, the Netherlands. [15]Department of Surgery, Catharina Hospital, Eindhoven, the Netherlands. [16]Department of Surgery, Dijklander Hospital, Hoorn, the Netherlands. [17]Department of Pediatric Surgery, Sophia Children's Hospital, Erasmus University Medical Center, Rotterdam, the Netherlands. [18]Department of Surgery, Flevo Hospital, Almere, the Netherlands. [19]Department of Surgery, Franciscus Gasthuis & Vlietland, Rotterdam, the Netherlands. [20]Department of Surgery, Gelre Hospitals, Apeldoorn/Zutphen, the Netherlands. [21]Department of Surgery, Haaglanden Medical Center, The Hague, the Netherlands. [22]Department of Pediatric Surgery, Juliana Children's Hospital, Haga Hospital, The Hague, the Netherlands. [23]Department of Surgery, IJsselland Hospital, Capelle aan den IJssel, the Netherlands. [24]Department of Surgery, Ikazia Hospital, Rotterdam, the Netherlands. [25]Department of Surgery, Isala, Zwolle, the Netherlands. [26]Department of Surgery, Laurentius Hospital, Roermond, the Netherlands. [27]Department of Surgery, Maasstad Hospital, Rotterdam, the Netherlands. [28]Department of Surgery, Maxima Medical Center, Veldhoven, The Netherlands. [29]Department of Surgery, Meander Medical Center, Amersfoort, the Netherlands. [30]Department of Surgery, University Medical Center Groningen, Groningen, the Netherlands. [31]Department of Surgery, Noordwest Ziekenhuisgroep, Alkmaar, the Netherlands. [32]Department of Surgery, OLVG, Amsterdam the Netherlands. [33]Department of Pediatric Surgery, Radboudumc -

Amalia Children's Hospital, Nijmegen, the Netherlands. [34]Department of Surgery, Reinier de Graaf Gasthuis, Delft, the Netherlands. [35]Department of Surgery, Rijnstate, Arnhem, the Netherlands. [36]Department of Surgery, Red Cross Hospital, Beverwijk, the Netherlands. [37]Department of Surgery, St. Antonius Hospital, Nieuwegein, the Netherlands. [38]Department of Surgery, Spaarne Gasthuis, Haarlem, the Netherlands. [39]Department of Surgery, Tergooi, Hilversum, the Netherlands. [40]Department of Pediatric Surgery, University Medical Center Groningen, Groningen, the Netherlands. [41]Department of Surgery, Zaans Medical Center, Zaandam, the Netherlands. [42]Department of Surgery, Amstelland Hospital, Amstelveen, the Netherlands. [43]Department of Surgery, Ziekenhuisgroep Twente, Almelo, the Netherlands. [44]Department of Surgery, Zuyderland Medical Center, Heerlen/Sittard, the Netherlands.

Authors' contributions: All authors have contributed to the design of the study protocol. The protocol was drafted by PvA, RRG and RB and refined by JHvdL, MCJvdW, RvE, JPMD, and LWEvH. Statistical advice was provided by JHvdL, MCJvdW, and RvE. The manuscript was drafted by PvA and refined by all other authors. All authors have read and approved the final manuscript. All local investigators who are responsible for the conduct of the study in the participating centers are acknowledged in the CAPP collaborative study group. They have all read and approved the final manuscript.

Funding: This work was supported by The Netherlands Organization for Health Research and Development (ZonMw) (grant number: 80-85009-98-2007).

Competing interests: None declared.

Box 1

Key points standardized treatment strategies		
Laparoscopic appendectomy	Open appendectomy	Non-operative treatment
Conventional laparoscopy (three-trocar technique)	Gridiron incision at McBurney	At least 48 hours of IV 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
Skelletizing of the mesoappendix with coagulation or clips	Appendiceal stump closure by ligation	The decision to perform percutaneously/surgically drainage of an appendiceal abscess is made by the treating surgeon
Appendiceal stump closure: Two endoloops. In case of involvement of the appendiceal base → endostapler	Closure of wounds as appropiate	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 2

Predefined discharge criteria
Discharge criteria equal for all treatment strategies: - Body temperature <38.0 - NRS<4 - Adequate oral intake - Able to mobilize
Additional discharge criteria for non-operative treatment strategy: - Decreased leukocytosis - Decreased C-reactive protein

Table 1. Baseline characteristics subgroup 1

Variable	Pre-weighting sample		*P*-value	Post-weighting 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)	Mean (SD)	*p* = 0.XX	Mean (SD)	Mean (SD)	*p* = 0.XX
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 (%)	N (% of Total)	N (% of Total)	*p* = 0.XX	N (% of Total)	N (% of Total)	*p* = 0.XX
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 (%)	N (% of Total)	N (% of Total)	*p* = 0.XX	N (% of Total)	N (% of Total)	*p* = 0.XX
Weekend presentation, n (%)	N (% of Total)	N (% of Total)	*p* = 0.XX	N (% of Total)	N (% of Total)	*p* = 0.XX
Duration of abdominal pain	Median (IQR)	Median (IQR)	*p* = 0.XX	Median (IQR)	Median (IQR)	*p* = 0.XX

Table 2. Baseline characteristics subgroup 2

Variable	Pre-weighting sample		*P*-value	Post-weighting sample		*P*-value
	Non-operative treatment, n	Direct appendectomy, n		Non-operative treatment, n	Direct 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)	Mean (SD)	*p* = 0.XX	Mean (SD)	Mean (SD)	*p* = 0.XX
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 (%)	N (% of Total)	N (% of Total)	*p* = 0.XX	N (% of Total)	N (% of Total)	*p* = 0.XX
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
	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 (%)	N (% of Total)	N (% of Total)	*p* = 0.XX	N (% of Total)	N (% of Total)	*p* = 0.XX
Weekend presentation, n (%)	N (% of Total)	N (% of Total)	*p* = 0.XX	N (% of Total)	N (% of Total)	*p* = 0.XX
Days of abdominal pain	Median (IQR)	Median (IQR)	*p* = 0.XX	Median (IQR)	Median (IQR)	*p* = 0.XX

Table 3. Primary outcome subgroup 1

	Laparoscopic appendectomy, n	Open appendectomy, n	Absolute difference in proportions	Unadjusted Odds Ratio (OR)	Propensity score adjusted absolute difference	*p*-value	Propensity score adjusted Odds Ratio	*p*-value
Complications after 3 months, n (%)	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	OR (95%CI)	Absolute	*p* = 0.XX	OR (95%CI)	*p* = 0.XX
Clavien-Dindo II	N (% of Total)	N (% of Total)	Difference	OR (95%CI)	Difference	*p* = 0.XX	OR (95%CI)	*p* = 0.XX
Clavien-Dindo III	N (% of Total)	N (% of Total)	(95% CI)	OR (95%CI)	(95% CI)	*p* = 0.XX	OR (95%CI)	*p* = 0.XX
Clavien-Dindo IV	N (% of Total)	N (% of Total)		OR (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 4. Primary outcome subgroup 2

	Non-operative treatment, n	Direct appendectomy, n	Absolute difference in proportions	Unadjusted Odds Ratio (OR)	Propensity score adjusted absolute difference	*p*-value	Propensity score adjusted Odds Ratio	*p*-value
Complications after 3 months, n (%)	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	OR (95%CI)	Absolute	*p* = 0.XX	OR (95%CI)	*p* = 0.XX
Clavien-Dindo II	N (% of Total)	N (% of Total)	Difference	OR (95%CI)	Difference	*p* = 0.XX	OR (95%CI)	*p* = 0.XX
Clavien-Dindo III	N (% of Total)	N (% of Total)	(95% CI)	OR (95%CI)	(95% CI)	*p* = 0.XX	OR (95%CI)	*p* = 0.XX
Clavien-Dindo IV	N (% of Total)	N (% of Total)		OR (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 wit abscess and/or mass formation

Table 5. Secondary outcomes subgroup 1

	Laparoscopic appendectomy, n	Open appendectomy, n	Unadjusted Odds Ratio (OR)	Propensity score adjusted Odds Ratio	*p*-value
Any complication					
Admission, n (%)	N (% of Total)	N (% of Total)	OR (95%CI)	OR (95%CI)	*p* = 0.XX
30-days, n (%)	N (% of Total)	N (% of Total)	OR (95%CI)	OR (95%CI)	*p* = 0.XX
Intra-abdominal abscess (at 3 months), n (%)	N (% of Total)	N (% of Total)	OR (95%CI)	OR (95%CI)	*p* = 0.XX
Superficial Site Infection (at 3 months), n (%)	N (% of Total)	N (% of Total)	OR (95%CI)	OR (95%CI)	*p* = 0.XX
Secondary/prolonged bowel obstruction (at 3 months), n (%)	N (% of Total)	N (% of Total)	OR (95%CI)	OR (95%CI)	*p* = 0.XX
Length of hospital stay (days)	Mean (SD)	Mean (SD)	Mean difference	Mean difference	*p* = 0.XX
Level of pain (during admission)	Mean (SD)	Mean (SD)	Mean difference	Mean difference	*p* = 0.XX
Extra visits to GP, outpatient clinic or ED	Mean (SD)	Mean (SD)	Mean difference	Mean difference	*p* = 0.XX
Hr-QoL (PedsQL 4.0)					
Admission	Mean (SD)	Mean (SD)	Mean	Mean difference	*p* = 0.XX
30 days	Mean (SD)	Mean (SD)	difference		*p* = 0.XX
3 months	Mean (SD)	Mean (SD)			*p* = 0.XX
Patient Satisfaction (3 months)					
NET Promoter Score	Mean (SD)	Mean (SD)	Mean	Mean difference	*p* = 0.XX
PSQ-18	Mean (SD)	Mean (SD)	difference		*p* = 0.XX
Direct costs (3 months)	Mean (SD)	Mean (SD)	Mean difference	Mean difference	*p* = 0.XX
Indirect costs (3 months)	Mean (SD)	Mean (SD)	Mean difference	Mean difference	*p* = 0.XX

GP: General Practitioner; ED: Emergency Department; Hr-QoL: Health-related Quality of Life; PSQ: Patient Satisfaction Questionnaire
^ This column presents the pooled/combined results of the five propensity score strata

Table 6. Secondary outcomes subgroup 2

	Non-operative treatment, n	Direct appendectomy, n	Unadjusted Odds Ratio (OR)	Propensity score adjusted Odds Ratio	*p*-value
Any complication					
Admission, n (%)	N (% of Total)	N (% of Total)	OR (95%CI)	OR (95%CI)	*p* = 0.XX
30-days, n (%)	N (% of Total)	N (% of Total)	OR (95%CI)	OR (95%CI)	*p* = 0.XX
Intra-abdominal abscess (at 3 months), n (%)	N (% of Total)	N (% of Total)	OR (95%CI)	OR (95%CI)	*p* = 0.XX
Superficial Site Infection (at 3 months), n (%)	N (% of Total)	N (% of Total)	OR (95%CI)	OR (95%CI)	*p* = 0.XX
Secondary/prolonged bowel obstruction (at 3 months), n (%)	N (% of Total)	N (% of Total)	OR (95%CI)	OR (95%CI)	*p* = 0.XX
Length of hospital stay (days)	Mean (SD)	Mean (SD)	Mean difference	Mean difference	*p* = 0.XX
Level of pain (during admission)	Mean (SD)	Mean (SD)	Mean difference	Mean difference	*p* = 0.XX
Extra visits to GP, outpatient clinic or emergency department	Mean (SD)	Mean (SD)	Mean difference	Mean difference	*p* = 0.XX
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.XX
30 days	Mean (SD)	Mean (SD)			*p* = 0.XX
3 months	Mean (SD)	Mean (SD)			*p* = 0.XX
Patient Satisfaction (3 months)					
NET Promoter Score	Mean (SD)	Mean (SD)	Mean difference	Mean difference	*p* = 0.XX
PSQ-18	Mean (SD)	Mean (SD)			*p* = 0.XX
Direct costs (3 months)	Mean (SD)	Mean (SD)	Mean difference	Mean difference	*p* = 0.XX
Indirect costs (3 months)	Mean (SD)	Mean (SD)	Mean difference	Mean difference	*p* = 0.XX

GP: General Practitioner; ED: Emergency Department; Hr-QoL: Health-related Quality of Life; PSQ: Patient Satisfaction Questionnaire
^ This column presents the pooled/combined results of the five propensity score strata

Appendix 1. Standardized treatment strategies

Subgroup 1 (complex appendicitis without enlarged mass and or abscess formation):

Laparoscopic appendectomy:

Patients are admitted to the pediatric (surgical) ward and pain medication and intravenous fluids are administered according to the national guideline.[13] [Bom] Antibiotic prophylaxis will be administered preoperatively consisting of a single dose (type of antibiotic according to local protocol). Laparoscopic appendectomy is performed according to daily practice but with the standardized key points as listed in box 1. Postoperative antibiotics are administered intravenously according to local protocol. If, after at least 48 hours of intravenous antibiotics, the patient is without fever for 24 hours, the decision can be made to change to oral antibiotics for a total length of five days. Discharge is allowed when the predefined discharge criteria have been met (Box 2).

Open appendectomy:

Pre- and postoperative care according to the same protocol as the laparoscopic appendectomy group. Open appendectomy is performed by a gridiron incision at McBurney's point and the appendiceal stump is closed by ligation.

Subgroup 2 (complex appendicitis with enlarged mass and or abscess formation):

Non-operative treatment:

Non-operative treatment consists of administration of intravenous antibiotics with or without drainage procedures (in case of abscess formation), reserving an appendectomy for those not responding or with recurrent disease. Antibiotic treatment consists of at least 48 hours of intravenous antibiotics. Proposed antibiotic regimens are a combination of amoxicillin/clavulanic acid 25/2.5mg/kg every six hours (maximum dose: 6000/600mg/day) and gentamicin (7mg/kg once daily) or a combination of intravenous cefuroxime 25mg/kg every six hours (maximum dose: 6000mg/day) and metronidazole 10mg/kg every eight hours

(maximum 4000mg/day). In case of an appendiceal abscess a drainage procedure can be performed either percutaneously or surgical. Prior to removal of the drainage tube imaging studies will be obtained to confirm complete resolution of the drained abscess.

Vital parameters are repeated every eight hours. Intravenous fluid is administered and pain medication prescribed according to the Dutch national guidelines.

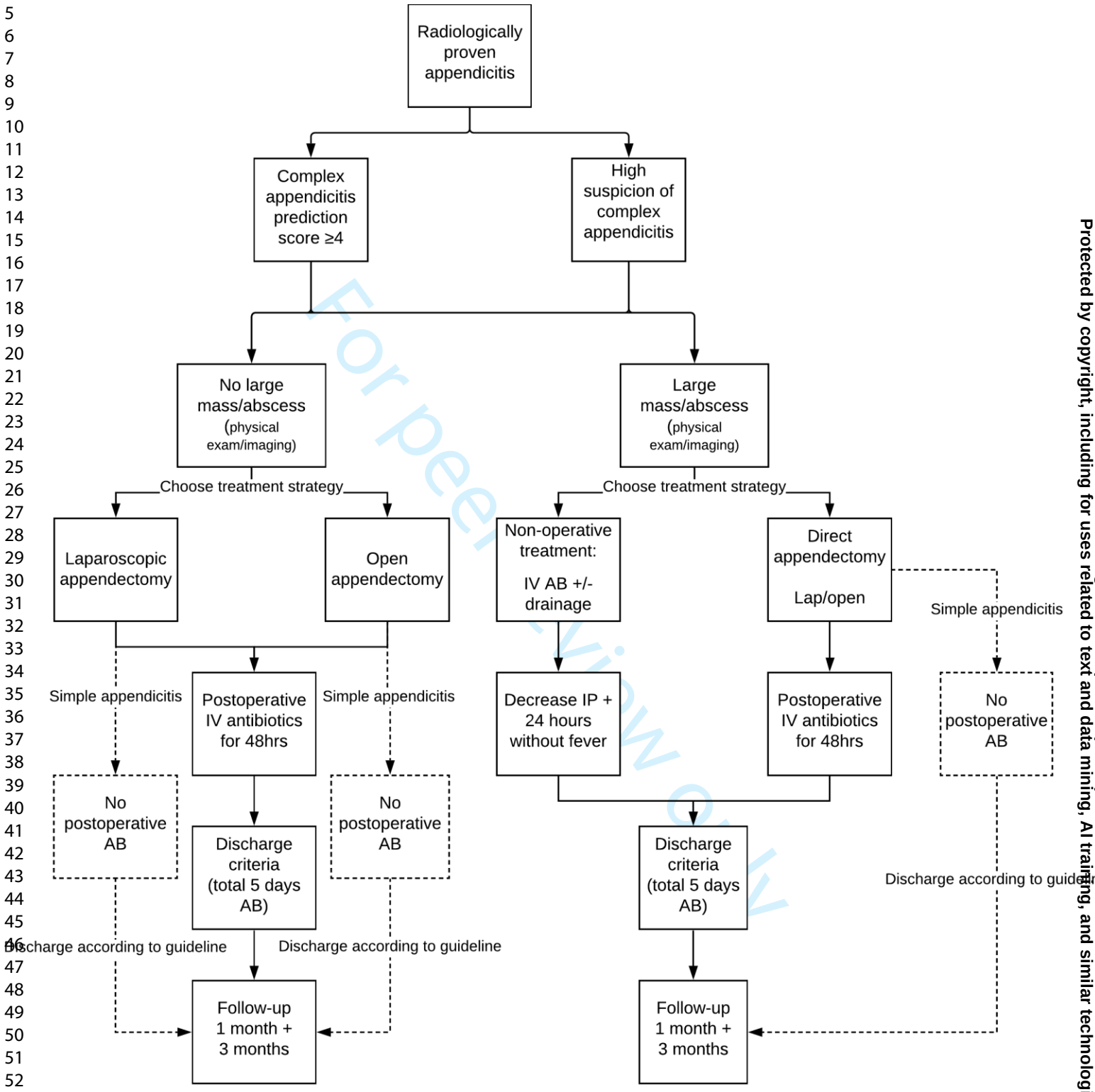
If the patient has received 48 hours of intravenous antibiotics, a decrease in infection parameters is noted, and the patient is at least 24 hours without fever, the decision can be made to change to oral antibiotics with a total length of antibiotic treatment of five days.

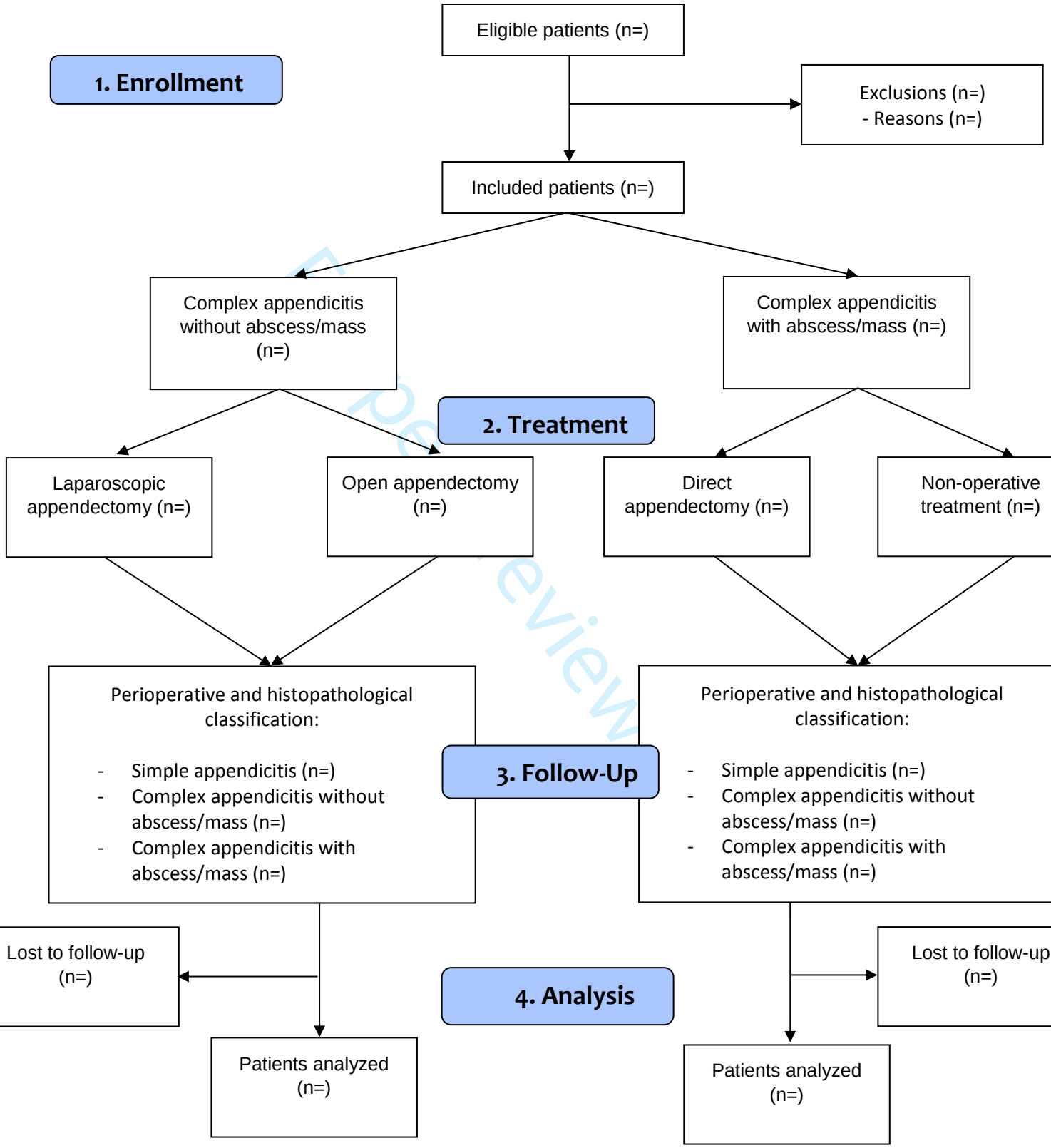
In case of clinical deterioration, additional imaging studies, additional drainage procedures or an appendectomy can be performed at any time. This decision is left at the treating surgeon's discretion, but consultation with the study coordinators on the appropriate course of action is possible.

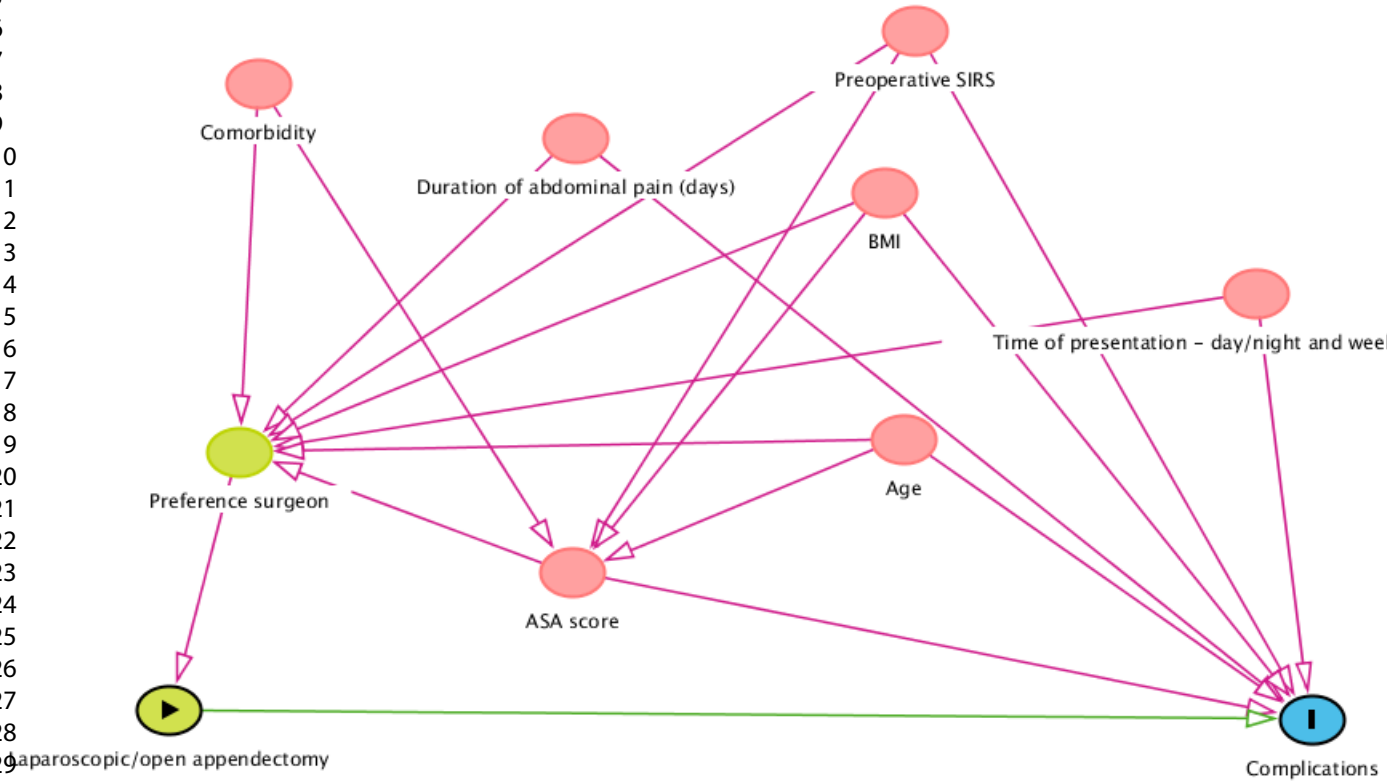
Discharge is allowed when the predefined discharge criteria have been met (Box 2).

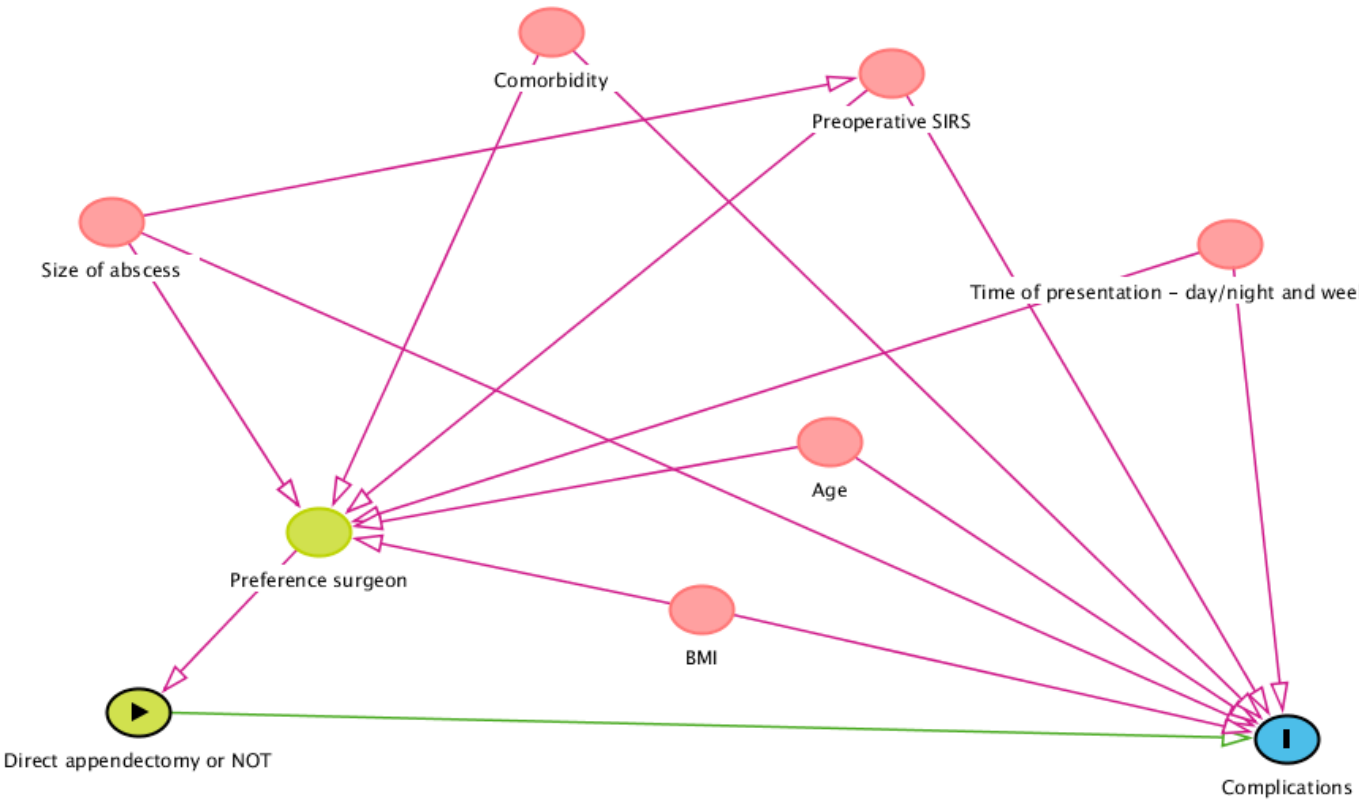
Operative treatment:

Laparoscopic and open appendectomy are performed as described for patients in subgroup 1.









Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cohortreporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	3-5
Objectives	#3	State specific objectives, including any prespecified hypotheses	5
Methods			

Study design	#4	Present key elements of study design early in the paper	5
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	6
Eligibility criteria	#6b	For matched studies, give matching criteria and number of exposed and unexposed	n/a
Variables	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-11
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	8-11
Bias	#9	Describe any efforts to address potential sources of bias	11-13
Study size	#10	Explain how the study size was arrived at	7-8
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	11-13
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	11-13
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	11-13
Statistical methods	#12c	Explain how missing data were addressed	11-13
Statistical methods	#12d	If applicable, explain how loss to follow-up was addressed	11-13

Statistical methods	#12e	Describe any sensitivity analyses	
11-13			
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	Figure 2
Participants	#13b	Give reasons for non-participation at each stage	Figure 2
Participants	#13c	Consider use of a flow diagram	
Figure 2			
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	Table 1 / Table 2
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	
Table 1-6			
Descriptive data	#14c	Summarise follow-up time (eg, average and total amount)	
9			
Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	
Table 3-6			
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 3-6
Main results	#16b	Report category boundaries when continuous variables were categorized	n/a

Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
n/a			
Other analyses	#17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11-13, Table 3-6
Discussion			
Key results	#18	Summarise key results with reference to study objectives	n/a
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	15-22
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	15-22
Generalisability	#21	Discuss the generalisability (external validity) of the study results	15-22
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	28

Notes:

- 14a: Table 1 / Table 2
- 17: 11-13, Table 3-6 The STROBE checklist is distributed under the terms of the Creative Commons Attribution License CC-BY. This checklist was completed on 23. June 2021 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

BMJ Open

The identification of the optimal treatment strategy for complex appendicitis in the pediatric population; a protocol for a multicenter prospective cohort study (CAPP study)

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-054826.R1
Article Type:	Protocol
Date Submitted by the Author:	05-Nov-2021
Complete List of Authors:	van Amstel, Paul; Emma Children's Hospital, Amsterdam UMC, University of Amsterdam & Vrije Universiteit Amsterdam, Department of Pediatric Surgery; Amsterdam UMC Location AMC Bakx, Roel; Emma Children's Hospital, Amsterdam UMC, University of Amsterdam, Department of Pediatric Surgery, Amsterdam, NL, Pediatric Surgery; Amsterdam UMC Locatie AMC van der Lee, Johanna H.; Amsterdam UMC, University of Amsterdam & Vrije Universiteit Amsterdam, Pediatric Clinical Research Office; Knowledge Institute of the Dutch Association of Medical Specialists van der Weide, Marijke C.; Amsterdam UMC, University of Amsterdam & Vrije Universiteit Amsterdam, Obstetrics and Gynaecology Eekelen, Rik; Amsterdam UMC Location AMC, Centre for Reproductive Medicine Derikx, Joep; Emma Children's Hospital, Amsterdam UMC, University of Amsterdam & Vrije Universiteit Amsterdam, Department of Pediatric Surgery; Amsterdam UMC Location AMC van Heurn, Ernest; Emma Children's Hospital, Amsterdam UMC, University of Amsterdam & Vrije Universiteit Amsterdam, Department of Pediatric Surgery; Amsterdam UMC Location AMC Gorter, Ramon R.; Emma Children's Hospital, Amsterdam UMC, University of Amsterdam & Vrije Universiteit Amsterdam, Department of Pediatric Surgery; Amsterdam UMC Location AMC
Primary Subject Heading:	Surgery
Secondary Subject Heading:	Paediatrics
Keywords:	PAEDIATRIC SURGERY, Paediatric colorectal surgery < PAEDIATRIC SURGERY, Paediatric gastroenterology < PAEDIATRICS

The identification of the optimal treatment strategy for complex appendicitis in the pediatric population; a protocol for a multicenter prospective cohort study (CAPP study)

Paul van Amstel[1], MD, Roel Bakx[1] MD PhD, Johanna H van der Lee[2], MD PhD, Marijke C van der Weide[3], MD PhD, Rik van Eekelen[4], MD PhD, Joep PM Derikx[1], MD PhD, LW Ernest van Heurn[1], MD PhD, Ramon R. Gorter[1], MD PhD, on behalf of the CAPP collaborative study group.

1. Emma Children's Hospital, Amsterdam UMC, University of Amsterdam & Vrije Universiteit Amsterdam, Department of Pediatric Surgery, Amsterdam, The Netherlands.
2. Amsterdam UMC, University of Amsterdam & Vrije Universiteit Amsterdam, Pediatric Clinical Research Office, Amsterdam, and Knowledge Institute of the Dutch Association of Medical Specialists, Utrecht, the Netherlands.
3. Amsterdam UMC, University of Amsterdam & Vrije Universiteit Amsterdam, Department of Obstetrics and Gynaecology, Amsterdam, the Netherlands.
4. Amsterdam UMC, location Academic Medical Centre, Centre for Reproductive Medicine, Amsterdam, the Netherlands.

Correspondence:

Name: P. van Amstel
Address: Emma Children's Hospital, Amsterdam UMC, University of Amsterdam & Vrije Universiteit Amsterdam, Department of Pediatric Surgery, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands.
Email: p.vanamstel@amsterdamumc.nl
Telephone: +31 20 56 65693
Fax: +31 20 444 2135

Abstract

Introduction: In daily practice large heterogeneity in the treatment of children with complex appendicitis exists. Complex appendicitis can be divided in 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-center, comparative, non-randomized 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 to laparoscopic appendectomy for children without appendiceal mass and/or abscess and initial non-operative treatment (i.e. 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 two years and nine months, a sample size of 1308 patients is aimed. Primary outcome is the proportion of patients experiencing any complication at three 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 (inter)national conferences.

Trial registration number: NCT04755179; NL9371

Strengths and limitations of this study

- Generalizable data gathered from a large cohort of children treated for acute complex appendicitis according to standardized treatment strategies in more than 30 academic and (large) teaching hospitals in the Netherlands.
- Study protocol designed by a multidisciplinary team consisting of epidemiologists, pediatricians, infectiologists, gastro-enterologists, (interventional) radiologists, patient support groups and (pediatric) 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-randomized study design potentially allows for confounding by indication.

Introduction

Acute appendicitis is one of the most common gastro-intestinal disorders with a lifetime incidence of 7-9%.[1 2] 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.[3] Insights in the pathogenesis of appendicitis have led to the recognition of two distinct types: simple (or uncomplicated) and complex (or complicated) appendicitis.[4-6] 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.[3] 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.[7 8] In recent times laparoscopic appendectomy is increasingly applied in both adults (80%) and children (60%).[3 9] Potential benefits reported for this approach (compared to 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, level of evidence on this topic is low and inconsistency in results is found between studies.[10]

Evidence regarding the treatment of children presenting with complex appendicitis with mass and/or abscess formation is scarce as well. Some surgeons favor 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 randomized 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.[11] 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 to direct appendectomy.[12] 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.[13]

The lack of high-quality data regarding the management of complex appendicitis in the pediatric population emphasizes the need for well-designed studies in order to identify the optimal treatment strategy for complex appendicitis in the pediatric population. The aim of this study is twofold; firstly, to evaluate the outcomes (in terms of complications, health-related Quality of Life, and costs) of open appendectomy compared to laparoscopic appendectomy for children with a complex appendicitis without appendiceal mass and/or abscess. Secondly to compare the outcomes (in terms of complications, health-related Quality of Life, and costs) of initial non-operative treatment (i.e. 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 at the 29th of January 2021 (NCT04755179) and the Netherlands Trial Register at the 4th of April 2021 (NL9371).

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-center, comparative, non-randomized prospective cohort study with standardized treatment strategies. The choice of treatment is jointly decided by the physician and the patient/parents, and subsequently a standardized treatment strategy is followed. Data are collected during admission, at one and three 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.[14]

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 upon imaging confirmed acute appendicitis and the following predefined criteria (regarding the severity of appendicitis):

- Four points or more on the complex appendicitis prediction score.[15]

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 pediatric scoring system that predicts the probability of complex appendicitis.[15] This scoring system with a scale ranging from 0 to 10, consists of five preoperative variables (each awarded points): diffuse abdominal guarding (three points), CRP level >38 mg/L (two points), signs of complex appendicitis on ultrasound (two points), temperature >37.5°C (one point), and more than one day of abdominal pain (two points). In an independent validation in a pediatric cohort, this scoring system had a diagnostic accuracy of 91% (95%CI: 84-98%), 90% (95%CI: 54-99%) sensitivity, 91% (95%CI: 79-97%) specificity, positive likelihood ratio of 10 (95%CI: 4.19-23.42) and negative likelihood ratio of 0.11 (95%CI: 0.02-0.71).[15]

Subgroups of complex appendicitis

Patients will be classified into the two subgroups of complex appendicitis based upon 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 categorized as subgroup 1 (complex appendicitis without abscess or mass). In this subgroup laparoscopic appendectomy will be compared to open appendectomy. If signs suggestive of intra-abdominal abscess and/or enlarged mass are present, patients will be categorized as subgroup 2 (complex appendicitis with abscess or mass). Initial non-operative treatment will be compared to 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 at the 12th of 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 two years and nine 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%.[3 9] 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.[13]

Sample size calculation

Based upon 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.

Standardized treatment strategies

Standardized treatment protocols were developed in order to reduce the heterogeneity in treatment between the participating hospitals. All participating sites agreed to conform to these standardized treatment protocols to the best of their ability. These standardized treatments are completely based on the recommendations given in the Dutch national guideline regarding the pre-, peri- and postoperative care. See Appendix 1 and Box 1 for a detailed description of the treatment strategies. All key points of the treatment strategies that are described in Box 1 and 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 three 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 categorize 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 gastro-intestinal decompression with a nasogastric tube.
- Anesthesia related complications, such as pneumonia
- Incisional hernia: Any abdominal wall gap with or without a bulge in the area of a postoperative scar 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 three 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 three months after inclusion
- Proportion of patients with a superficial site infection within three months after inclusion

- Proportion of patients with a secondary/prolonged bowel obstruction within three months after inclusion
- Proportion of patients not having to undergo appendectomy within three months after inclusion
- Proportion of patients experiencing recurrent appendicitis within three 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 three months after inclusion (histopathologically no sign of recurrent appendicitis)

Patient-related endpoints:

- Level of pain: assessed by the Numeric Rating Scale (NRS) and total use of pain medication during admission
- Health-related Quality of Life 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 three 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 three 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 three 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, 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 (Figure 3 and Figure 4). Identified variables for subgroup 1 are age, 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 pre-operatively using standardized 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 linearized propensity score will be compared between treatment groups. Balancing will be assessed by comparing the standardized 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 standardized 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 1 and 2. Data will be presented using absolute numbers and percentages for discrete outcomes. Continuous outcomes will be presented as means with standard deviation or medians with interquartile ranges, according to their distribution. Baseline characteristics will be compared between treatment groups and presented for both the pre-matching cohort and post-matching cohort. For each subgroup of complex appendicitis a baseline characteristics table will be created.

Primary endpoint analysis

Proportion of complications after three 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 3 and 4.

Unadjusted and propensity score adjusted differences in proportions and odds ratios (OR) will be presented with their 95% confidence intervals.

Secondary endpoints analysis

Data on the secondary outcomes will be presented as displayed in tables 5 and 6.

Unadjusted and propensity score adjusted odds ratios 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, one month, and three months. In this way both the child's and parents' perspective will be assessed. No difference in effect is anticipated after three months, as acute appendicitis is an acute disease with a relatively short period of disutility.

Costs will be assessed from the societal perspective, integrating health care 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, one month, and three 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 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 €20,000 / QALY. QALY's will be calculated using the EQ 5D youth and EQ-5D-Proxy questionnaires. As acute appendicitis is an acute disease, disutility might be short term in our study. Therefore, QALY's will be transformed to quality-adjusted life months (QALMs).

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 five 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 (i.e. healthcare professionals, patients and parents, and insurance companies).

Cost analysis

Identification of all health care related costs will be recorded per patient. Potential determinants influencing the budget impact analysis 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 spread sheet will be used in which obtained data is inserted. At completion

of this study, based upon 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 health care budget per annum for the Netherlands in terms of cost reduction.

Ethics 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 is handled confidentially in accordance with the General Data Protection Regulation. Castor Electronic Data Capture will be used for data collection and storage.[27] 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 onsite monitoring of participating sites by an independent and qualified monitor.

Ethics

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 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 pediatric 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 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 pediatric 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.[10 12 28] Evidence for (the optimal treatment strategy in) children that present with complex appendicitis without mass or abscess is also relatively scarce. Only two small 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.[10 29 30] The heterogeneity in current daily practice reflects the lack of evidence and emphasizes the need for well-designed studies.

Choice of study design

The CAPP study is a nation-wide 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 (i.e. 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, pediatricians, infectiologists, gastro-enterologists, (interventional) radiologists, patient support groups and (pediatric) surgeons. The nationwide and multidisciplinary character of this study is potentially beneficial for implementation and results will be generalizable 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 generalizable 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 a Randomized Clinical Trial (RCT). However, before the start of the CAPP study, we conducted a nationwide survey that pointed out that there was reluctance amongst (pediatric) surgeons to participate in an RCT comparing these different treatment strategies in the pediatric 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 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.[31] 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 pre-operative 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 standardized treatment strategies steps were taken to reduce heterogeneity in treatment between hospitals. All key points of these standardized treatment strategies are based on the recommendations of the Dutch national guideline. These measures will improve comparability of results of the participating hospitals.

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 (i.e. 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 in- 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.[15] 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, generalized peritonitis, and an appendiceal mass or abscess.[23 32 33] 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 peri- and postoperative variables, i.e. the classification suggested by Bhangu et al.[23]

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.[14] 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 upon previous qualitative studies investigating possible promoting and obstructing factors for implementation, we decided to choose the proportion of patients experiencing complications within three months after the start of treatment as primary outcome. In addition, we think that 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 health-related quality of life 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, i.e. death, physiological/clinical manifestations, life impact, resource use and adverse events. Besides

our primary outcome (overall complication rate), life impact outcomes (i.e. pediatric quality of life, return to school or normal activities) and resource use outcomes (i.e. 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 three 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%.[34] Furthermore, as appendicitis is an acute disease it is expected to affect health-related quality of life and medical costs for only a short period of time. As it is expected that the majority of children is recovered within three months, a follow-up duration of three 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 three 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 randomized controlled trial has been published recently in which children treated non-operatively for appendix mass were randomized between active observation or planned interval appendectomy.[35] This study showed a rate of 6% severe complications after interval appendectomy, whereas only 12% of children under active observation developed recurrent appendicitis within one year follow-up. Therefore, interval appendectomy was not incorporated as a routine procedure after non-operative treatment in the CAPP study. Opponents of this strategy point to the possibility of missing neuro-endocrine tumors (NETs) of the appendix. However, several studies have shown that NETs are rarely found at histopathological examination (0-0.4%).[36-39]

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.[40-42] As the CAPP study only has a follow-up period of three 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 pediatric population.

Figure 1. Flowchart of standardized treatment protocol

Figure 2. Patient flowchart

Figure 3. Direct Acyclic Graphs subgroup 1

Figure 4. Direct Acyclic Graphs subgroup 2

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(5):910-25. doi: 10.1093/oxfordjournals.aje.a115734 [published Online First: 1990/11/01]
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(12):2787-94. doi: 10.1007/s00268-012-1749-z [published Online First: 2012/09/06]
3. van Rossem CC, Bolmers MD, Schreinemacher MH, et al. Prospective nationwide outcome audit of surgery for suspected acute appendicitis. *Br J Surg* 2016;103(1):144-51. doi: 10.1002/bjs.9964 [published Online First: 2015/10/29]
4. Andersson 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(1):86-92. doi: 10.1007/s00268-006-0056-y [published Online First: 2006/12/21]
5. Cobben LP, de Van Otterloo AM, Puylaert JB. Spontaneously resolving appendicitis: frequency and natural history in 60 patients. *Radiology* 2000;215(2):349-52. doi: 10.1148/radiology.215.2.r00ma08349 [published Online First: 2000/05/05]
6. Ruber M, Andersson M, Petersson BF, et al. Systemic Th17-like cytokine pattern in gangrenous appendicitis but not in phlegmonous appendicitis. *Surgery* 2010;147(3):366-72. doi: 10.1016/j.surg.2009.09.039 [published Online First: 2009/11/07]
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(1):27. doi: 10.1186/s13017-020-00306-3 [published Online First: 2020/04/17]
8. Gorter RR, Eker HH, Gorter-Stam MA, et al. Diagnosis and management of acute appendicitis. EAES consensus development conference 2015. *Surg Endosc* 2016;30(11):4668-90. doi: 10.1007/s00464-016-5245-7 [published Online First: 2016/10/28]
9. Bolmers 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(5):543-51. doi: 10.1007/s00383-018-4244-2 [published Online First: 2018/03/11]
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(10):1993-2004. doi: 10.1007/s11605-012-1962-y [published Online First: 2012/07/20]
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. doi: 10.1002/14651858.CD011670.pub2 [published Online First: 2017/06/03]
12. Simillis C, Symeonides P, Shorthouse AJ, et al. A meta-analysis comparing conservative treatment versus acute appendectomy for complicated appendicitis (abscess or phlegmon). *Surgery* 2010;147(6):818-29. doi: 10.1016/j.surg.2009.11.013 [published Online First: 2010/02/13]
13. Bom WJ, Knaapen M, Gorter RR, et al. [Revised guideline for acute appendicitis. Amendments to diagnostics and treatment]. *Ned Tijdschr Geneeskd* 2020;164 [published Online First: 2020/05/15]
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(5):e028861. doi: 10.1136/bmjopen-2018-028861 [published Online First: 2019/05/28]
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(2):452-9. doi: 10.1016/j.jss.2015.08.042 [published Online First: 2015/10/06]

16. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004;240(2):205-13. doi: 10.1097/01.sla.0000133083.54934.ae [published Online First: 2004/07/27]
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(8):784-91. doi: 10.1001/jamasurg.2017.0904 [published Online First: 2017/05/04]
18. Varni JW, Seid M, Rode CA. The PedsQL™: Measurement Model for the Pediatric Quality of Life Inventory. *Medical Care* 1999;37(2):126-39.
19. Wille N, Badia X, Bonsel G, et al. Development of the EQ-5D-Y: a child-friendly version of the EQ-5D. *Qual Life Res* 2010;19(6):875-86. doi: 10.1007/s11136-010-9648-y [published Online First: 2010/04/21]
20. Thayaparan AJ, Mahdi E. The Patient Satisfaction Questionnaire Short Form (PSQ-18) as an adaptable, reliable, and validated tool for use in various settings. *Med Educ Online* 2013;18:21747. doi: 10.3402/meo.v18i0.21747 [published Online First: 2013/07/26]
21. Bouwmans C, Hakkaart-van Roijen L, Koopmanschap M, et al. Handleiding iMTA medical cost questionnaire (iMCQ). *Rotterdam: iMTA, Erasmus Universiteit Rotterdam* 2013
22. Bouwmans C, Krol M, Severens H, et al. The iMTA Productivity Cost Questionnaire: A Standardized Instrument for Measuring and Valuing Health-Related Productivity Losses. *Value Health* 2015;18(6):753-8. doi: 10.1016/j.jval.2015.05.009 [published Online First: 2015/09/28]
23. Bhangu A, Søreide K, Di Saverio S, et al. Acute appendicitis: modern understanding of pathogenesis, diagnosis, and management. *The Lancet* 2015;386(10000):1278-87. doi: 10.1016/s0140-6736(15)00275-5
24. PR R, DB R. The central role of the propensity score in observational studies for causal effects. *Biometrika* 1983;70(1):41-55.
25. Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. *Multivariate Behavioral Research* 2011;46(3):399-424. doi: 10.1080/00273171.2011.568786
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(28):3661-79. doi: 10.1002/sim.6607 [published Online First: 2015/08/05]
27. Castor EDC. Castor Electronic Data Capture 2019 [27 Aug. 2019]. Available from: https://castoredc.com accessed August 28, 2019.
28. van Amstel P, Sluckin TC, van Amstel T, et al. Management of appendiceal mass and abscess in children; early appendectomy or initial non-operative treatment? A systematic review and meta-analysis. *Surg Endosc* 2020;34(12):5234-49. doi: 10.1007/s00464-020-07822-y [published Online First: 2020/07/28]
29. Lintula H, Kokki H, Vanamo K, et al. Laparoscopy in children with complicated appendicitis. *J Pediatr Surg* 2002;37(9):1317-20. doi: 10.1053/jpsu.2002.34998 [published Online First: 2002/08/24]
30. Oka T, Kurkchubasche AG, Bussey JG, et al. Open and laparoscopic appendectomy are equally safe and acceptable in children. *Surg Endosc* 2004;18(2):242-5. doi: 10.1007/s00464-003-8140-y [published Online First: 2003/12/24]
31. Minneci PC, Hade EM, Lawrence AE, et al. Association of Nonoperative Management Using Antibiotic Therapy vs Laparoscopic Appendectomy With Treatment Success and Disability Days in Children With Uncomplicated Appendicitis. *Jama* 2020;324(6):581-93. doi: 10.1001/jama.2020.10888 [published Online First: 2020/07/31]
32. Blakely ML, Williams R, Dassinger MS, et al. Early vs interval appendectomy for children with perforated appendicitis. *Arch Surg* 2011;146(6):660-5. doi: 10.1001/archsurg.2011.6 [published Online First: 2011/02/23]

33. St Peter SD, Sharp SW, Holcomb GW, 3rd, et al. An evidence-based definition for perforated appendicitis derived from a prospective randomized trial. *J Pediatr Surg* 2008;43(12):2242-5. doi: 10.1016/j.jpedsurg.2008.08.051 [published Online First: 2008/12/02]
34. Rasmussen T, Fonnes S, Rosenberg J. Long-Term Complications of Appendectomy: A Systematic Review. *Scand J Surg* 2018;107(3):189-96. doi: 10.1177/1457496918772379 [published Online First: 2018/05/17]
35. Hall NJ, Eaton S, Stanton MP, et al. Active observation versus interval appendicectomy after successful non-operative treatment of an appendix mass in children (CHINA study): an open-label, randomised controlled trial. *The Lancet Gastroenterology & Hepatology* 2017;2(4):253-60. doi: 10.1016/s2468-1253(16)30243-6
36. Fouad D, Kauffman JD, Chandler NM. Pathology findings following interval appendectomy: Should it stay or go? *J Pediatr Surg* 2020;55(4):737-41. doi: 10.1016/j.jpedsurg.2019.05.001 [published Online First: 2019/05/28]
37. Gorter RR, van Amstel P, van der Lee JH, et al. Unexpected findings after surgery for suspected appendicitis rarely change treatment in pediatric patients; Results from a cohort study. *J Pediatr Surg* 2017;52(8):1269-72. doi: 10.1016/j.jpedsurg.2017.02.012 [published Online First: 2017/03/18]
38. Kim SS, Kays DW, Larson SD, et al. Appendiceal carcinoids in children--management and outcomes. *J Surg Res* 2014;192(2):250-3. doi: 10.1016/j.jss.2014.06.031 [published Online First: 2014/07/21]
39. Otake S, Suzuki N, Takahashi A, et al. Histological analysis of appendices removed during interval appendectomy after conservative management of pediatric patients with acute appendicitis with an inflammatory mass or abscess. *Surg Today* 2014;44(8):1400-5. doi: 10.1007/s00595-014-0950-0 [published Online First: 2014/06/17]
40. Ein SH, Langer JC, Daneman A. Nonoperative management of pediatric ruptured appendix with inflammatory mass or abscess: presence of an appendicolith predicts recurrent appendicitis. *J Pediatr Surg* 2005;40(10):1612-5. doi: 10.1016/j.jpedsurg.2005.06.001 [published Online First: 2005/10/18]
41. Mahida JB, Lodwick DL, Nacion KM, et al. High failure rate of nonoperative management of acute appendicitis with an appendicolith in children. *J Pediatr Surg* 2016;51(6):908-11. doi: 10.1016/j.jpedsurg.2016.02.056 [published Online First: 2016/03/29]
42. Tanaka Y, Uchida H, Kawashima H, et al. Long-term outcomes of operative versus nonoperative treatment for uncomplicated appendicitis. *J Pediatr Surg* 2015;50(11):1893-7. doi: 10.1016/j.jpedsurg.2015.07.008 [published Online First: 2015/08/12]

Collaborators: The CAPP collaborative study group includes the following contributors: H.A. Rippen[5], J. Berkhof[6], B.G.P. Koot[7], M. van der Kuip[8], R.R. van Rijn[9], H.J. Bonjer[10], J. Jansen[11], M.A. Lijkwan[12], G.D. Musters[12], P. Boele van Hensbroek[13], M. Springer[13], F.C. van Eijck[14], M.D.P. Luyer[15], A. Jairam[15], L.M. de Widt[16], M. Knaapen[16], C.M.G. Keyzer-Dekker[17], R.M.H. Wijnen[17], G.M.P. Diepenhorst[18], K.M.A. Dreuning[18], M.M. Poelman[19], D. Verver[19], P. van Duijvendijk[20], M.E. van der Sande[20], J.W.A. Oosterhuis[21], G.W. Zijp[22], E.H. Pasveer[22], R.P.R. Groenendijk[23], J.L.A. van Vugt[23], W.J. Vles[24], C.A. Selles[24], V.B. Nieuwenhuijs[25], J.T. Hoffman[25], J.W.A. Leijtens[26], E.G.M. Vosbeek[26], C.C. van Rossem[27], M.P. Gaspersz[27], M.H.M. Bender[28], B.J. Corten[28], E.C.J. Consten[29 30], M.F.J. Seesing[29], T.S. Bijlsma[31], S.M.L. The[31], L.E. Janssen[31], V.J. Leijdekkers[32], M.V. Nijenhuis[32], S.M.B.I. Botden[33], M. Joosten[33], A.L.A. Bloemendaal[34], C.F.J.M. Blanken-Peeters[35], W.M. IJgosse[35], A. Meij-de Vries[36], M.M. Bruntink[36], P.M.N.Y.H. Go[37], M. Pool[37], S.J. Oosterling[38], T.C. Derksen[38], A.A.W. van Geloven[39], T.T. Poels[39], J.B.F. Hulscher[40], F.C. den Boer[41], S.F. Hardon[41], F.P. Garssen[42], T. Wagner[42], M.F. Lutke Holzik[43], M.B.G.M. Decaestecker[43], E.G. Boerma[44], D. Schweitzer[44]. The surgical, pediatric, radiology, and emergency departments of the following hospitals contribute to the execution of this study: Amsterdam University Medical Centers, Amsterdam, the Netherlands; Admiraal de Ruyter Hospital, Goes, the Netherlands; Albert Schweitzer Hospital, Dordrecht, the Netherlands; Amphia, Breda, the Netherlands; Bravis Hospital, Bergen op Zoom, the Netherlands; Catharina Hospital, Eindhoven, the Netherlands; Dijklander Hospital, Hoorn, the Netherlands; Erasmus Medical Center, Rotterdam, the Netherlands; Flevo Hospital, Almere, the Netherlands; Franciscus Gasthuis & Vlietland, Rotterdam, the Netherlands; Gelre Hospitals, Apeldoorn/Zutphen, the Netherlands; Haaglanden Medical Center, The Hague, the Netherlands; Haga Hospital, The Hague, the Netherlands; IJsselland Hospital, Capelle aan den IJssel, the Netherlands; Ikazia Hospital, Rotterdam, the Netherlands; Isala, Zwolle, the Netherlands; Laurentius Hospital, Roermond, the Netherlands; Maasstad Hospital, Rotterdam, the Netherlands; Maxima Medical Center, Veldhoven, The Netherlands; Meander Medical Center, Amersfoort, the Netherlands; Noordwest Ziekenhuisgroep, Alkmaar, the Netherlands; OLVG, Amsterdam the Netherlands; Radboudumc, Nijmegen, the Netherlands; Reinier de Graaf Gasthuis, Delft, the Netherlands; Rijnstate, Arnhem, the Netherlands; Red Cross Hospital, Beverwijk, the Netherlands; St. Antonius Hospital, Nieuwegein, the Netherlands; Spaarne Gasthuis, Haarlem, the Netherlands; Tergooi, Hilversum, the Netherlands; University Medical Center Groningen, Groningen, the Netherlands; Zaans Medical Center, Zaandam, the Netherlands;

Amstelland Hospital, Amstelveen, the Netherlands; Ziekenhuisgroep Twente, Almelo, the Netherlands; Zuyderland Medical Center, Heerlen/Sittard, the Netherlands.

Affiliations:

[5]Dutch Child and Hospital Foundation, Utrecht, the Netherlands. [6]Department of Epidemiology and Biostatistics, VU University Medical Center, Amsterdam, the Netherlands. [7]Department of Pediatric Gastroenterology, Emma Children's Hospital, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands. [8]Department of Pediatric Infectious Diseases and Immunology, Emma Children's Hospital, Amsterdam UMC, Amsterdam, the Netherlands. [9]Department of Radiology and Nuclear Medicine, Emma Children's Hospital, University of Amsterdam, Amsterdam, the Netherlands. [10]Department of Surgery, Amsterdam UMC, University of Amsterdam & Vrije Universiteit Amsterdam, Amsterdam, the Netherlands. [11]Department of Surgery, Admiraal de Ruyter Hospital, Goes, the Netherlands. [12]Department of Surgery, Albert Schweitzer Hospital, Dordrecht, the Netherlands. [13]Department of Surgery, Amphia, Breda, the Netherlands. [14]Department of Surgery, Bravis Hospital, Bergen op Zoom, the Netherlands. [15]Department of Surgery, Catharina Hospital, Eindhoven, the Netherlands. [16]Department of Surgery, Dijklander Hospital, Hoorn, the Netherlands. [17]Department of Pediatric Surgery, Sophia Children's Hospital, Erasmus University Medical Center, Rotterdam, the Netherlands. [18]Department of Surgery, Flevo Hospital, Almere, the Netherlands. [19]Department of Surgery, Franciscus Gasthuis & Vlietland, Rotterdam, the Netherlands. [20]Department of Surgery, Gelre Hospitals, Apeldoorn/Zutphen, the Netherlands. [21]Department of Surgery, Haaglanden Medical Center, The Hague, the Netherlands. [22]Department of Pediatric Surgery, Juliana Children's Hospital, Haga Hospital, The Hague, the Netherlands. [23]Department of Surgery, IJsselland Hospital, Capelle aan den IJssel, the Netherlands. [24]Department of Surgery, Ikazia Hospital, Rotterdam, the Netherlands. [25]Department of Surgery, Isala, Zwolle, the Netherlands. [26]Department of Surgery, Laurentius Hospital, Roermond, the Netherlands. [27]Department of Surgery, Maasstad Hospital, Rotterdam, the Netherlands. [28]Department of Surgery, Maxima Medical Center, Veldhoven, The Netherlands. [29]Department of Surgery, Meander Medical Center, Amersfoort, the Netherlands. [30]Department of Surgery, University Medical Center Groningen, Groningen, the Netherlands. [31]Department of Surgery, Noordwest Ziekenhuisgroep, Alkmaar, the Netherlands. [32]Department of Surgery, OLVG, Amsterdam the Netherlands. [33]Department of Pediatric Surgery, Radboudumc -

Amalia Children's Hospital, Nijmegen, the Netherlands. [34]Department of Surgery, Reinier de Graaf Gasthuis, Delft, the Netherlands. [35]Department of Surgery, Rijnstate, Arnhem, the Netherlands. [36]Department of Surgery, Red Cross Hospital, Beverwijk, the Netherlands. [37]Department of Surgery, St. Antonius Hospital, Nieuwegein, the Netherlands. [38]Department of Surgery, Spaarne Gasthuis, Haarlem, the Netherlands. [39]Department of Surgery, Tergooi, Hilversum, the Netherlands. [40]Department of Pediatric Surgery, University Medical Center Groningen, Groningen, the Netherlands. [41]Department of Surgery, Zaans Medical Center, Zaandam, the Netherlands. [42]Department of Surgery, Amstelland Hospital, Amstelveen, the Netherlands. [43]Department of Surgery, Ziekenhuisgroep Twente, Almelo, the Netherlands. [44]Department of Surgery, Zuyderland Medical Center, Heerlen/Sittard, the Netherlands.

Authors' contributions: All authors have contributed to the design of the study protocol. The protocol was drafted by PvA, RRG and RB and refined by JHvdL, MCJvdW, RvE, JPMD, and LWEvH. Statistical advice was provided by JHvdL, MCJvdW, and RvE. The manuscript was drafted by PvA and refined by all other authors. All authors have read and approved the final manuscript. All local investigators who are responsible for the conduct of the study in the participating centers are acknowledged in the CAPP collaborative study group. They have all read and approved the final manuscript.

Funding: This work was supported by The Netherlands Organization for Health Research and Development (ZonMw) (grant number: 80-85009-98-2007).

Competing interests: None declared.

Box 1

Key points standardized treatment strategies		
Laparoscopic appendectomy	Open appendectomy	Non-operative treatment
Conventional laparoscopy (three-trocar technique)	Gridiron incision at McBurney	At least 48 hours of IV 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
Skelletizing of the mesoappendix with coagulation or clips	Appendiceal stump closure by ligation	The decision to perform percutaneously/surgically drainage of an appendiceal abscess is made by the treating surgeon
Appendiceal stump closure: Two endoloops. In case of involvement of the appendiceal base → endostapler	Closure of wounds as appropiate	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 2

Predefined discharge criteria
Discharge criteria equal for all treatment strategies: - Body temperature <38.0 - NRS<4 - Adequate oral intake - Able to mobilize
Additional discharge criteria for non-operative treatment strategy: - Decreased leukocytosis - Decreased C-reactive protein

Table 1. Baseline characteristics subgroup 1

Variable	Pre-weighting sample		*P*-value	Post-weighting 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)	Mean (SD)	*p* = 0.XX	Mean (SD)	Mean (SD)	*p* = 0.XX
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 (%)	N (% of Total)	N (% of Total)	*p* = 0.XX	N (% of Total)	N (% of Total)	*p* = 0.XX
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 (%)	N (% of Total)	N (% of Total)	*p* = 0.XX	N (% of Total)	N (% of Total)	*p* = 0.XX
Weekend presentation, n (%)	N (% of Total)	N (% of Total)	*p* = 0.XX	N (% of Total)	N (% of Total)	*p* = 0.XX
Duration of abdominal pain	Median (IQR)	Median (IQR)	*p* = 0.XX	Median (IQR)	Median (IQR)	*p* = 0.XX

Table 2. Baseline characteristics subgroup 2

Variable	Pre-weighting sample		*P*-value	Post-weighting sample		*P*-value
	Non-operative treatment, n	Direct appendectomy, n		Non-operative treatment, n	Direct 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)	Mean (SD)	*p* = 0.XX	Mean (SD)	Mean (SD)	*p* = 0.XX
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 (%)	N (% of Total)	N (% of Total)	*p* = 0.XX	N (% of Total)	N (% of Total)	*p* = 0.XX
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
	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 (%)	N (% of Total)	N (% of Total)	*p* = 0.XX	N (% of Total)	N (% of Total)	*p* = 0.XX
Weekend presentation, n (%)	N (% of Total)	N (% of Total)	*p* = 0.XX	N (% of Total)	N (% of Total)	*p* = 0.XX
Days of abdominal pain	Median (IQR)	Median (IQR)	*p* = 0.XX	Median (IQR)	Median (IQR)	*p* = 0.XX

Table 3. Primary outcome subgroup 1

	Laparoscopic appendectomy, n	Open appendectomy, n	Absolute difference in proportions	Unadjusted Odds Ratio (OR)	Propensity score adjusted absolute difference	*p*-value	Propensity score adjusted Odds Ratio	*p*-value
Complications after 3 months, n (%)	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	OR (95%CI)	Absolute	*p* = 0.XX	OR (95%CI)	*p* = 0.XX
Clavien-Dindo II	N (% of Total)	N (% of Total)	Difference	OR (95%CI)	Difference	*p* = 0.XX	OR (95%CI)	*p* = 0.XX
Clavien-Dindo III	N (% of Total)	N (% of Total)	(95% CI)	OR (95%CI)	(95% CI)	*p* = 0.XX	OR (95%CI)	*p* = 0.XX
Clavien-Dindo IV	N (% of Total)	N (% of Total)		OR (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 4. Primary outcome subgroup 2

	Non-operative treatment, n	Direct appendectomy, n	Absolute difference in proportions	Unadjusted Odds Ratio (OR)	Propensity score adjusted absolute difference	*p*-value	Propensity score adjusted Odds Ratio	*p*-value
Complications after 3 months, n (%)	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	OR (95%CI)	Absolute	*p* = 0.XX	OR (95%CI)	*p* = 0.XX
Clavien-Dindo II	N (% of Total)	N (% of Total)	Difference	OR (95%CI)	Difference	*p* = 0.XX	OR (95%CI)	*p* = 0.XX
Clavien-Dindo III	N (% of Total)	N (% of Total)	(95% CI)	OR (95%CI)	(95% CI)	*p* = 0.XX	OR (95%CI)	*p* = 0.XX
Clavien-Dindo IV	N (% of Total)	N (% of Total)		OR (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 wit abscess and/or mass formation

Table 5. Secondary outcomes subgroup 1

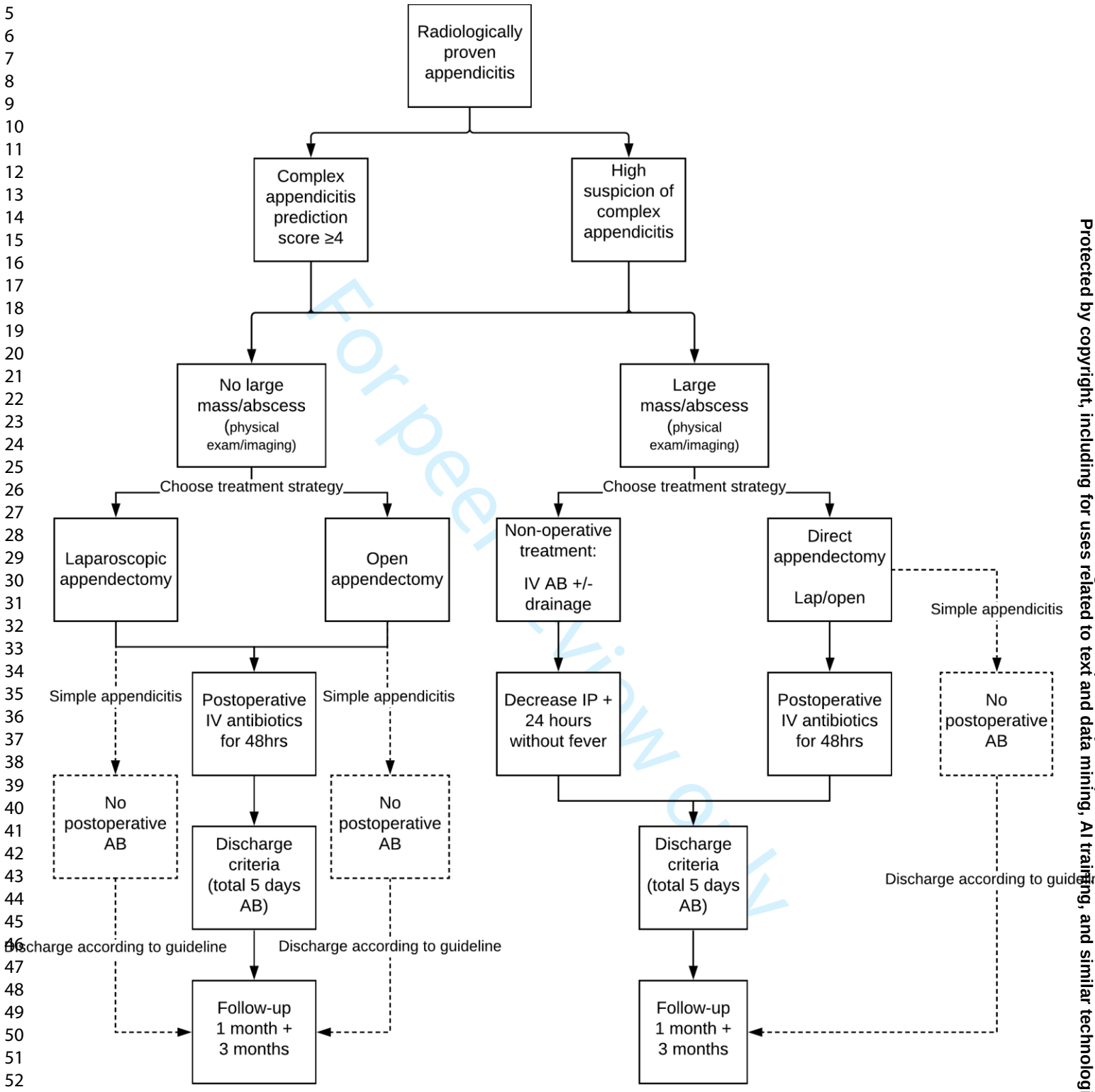
	Laparoscopic appendectomy, n	Open appendectomy, n	Unadjusted Odds Ratio (OR)	Propensity score adjusted Odds Ratio	*p*-value
Any complication					
Admission, n (%)	N (% of Total)	N (% of Total)	OR (95%CI)	OR (95%CI)	*p* = 0.XX
30-days, n (%)	N (% of Total)	N (% of Total)	OR (95%CI)	OR (95%CI)	*p* = 0.XX
Intra-abdominal abscess (at 3 months), n (%)	N (% of Total)	N (% of Total)	OR (95%CI)	OR (95%CI)	*p* = 0.XX
Superficial Site Infection (at 3 months), n (%)	N (% of Total)	N (% of Total)	OR (95%CI)	OR (95%CI)	*p* = 0.XX
Secondary/prolonged bowel obstruction (at 3 months), n (%)	N (% of Total)	N (% of Total)	OR (95%CI)	OR (95%CI)	*p* = 0.XX
Length of hospital stay (days)	Mean (SD)	Mean (SD)	Mean difference	Mean difference	*p* = 0.XX
Level of pain (during admission)	Mean (SD)	Mean (SD)	Mean difference	Mean difference	*p* = 0.XX
Extra visits to GP, outpatient clinic or ED	Mean (SD)	Mean (SD)	Mean difference	Mean difference	*p* = 0.XX
Hr-QoL (PedsQL 4.0)					
Admission	Mean (SD)	Mean (SD)	Mean	Mean difference	*p* = 0.XX
30 days	Mean (SD)	Mean (SD)	difference		*p* = 0.XX
3 months	Mean (SD)	Mean (SD)			*p* = 0.XX
Patient Satisfaction (3 months)					
NET Promoter Score	Mean (SD)	Mean (SD)	Mean	Mean difference	*p* = 0.XX
PSQ-18	Mean (SD)	Mean (SD)	difference		*p* = 0.XX
Direct costs (3 months)	Mean (SD)	Mean (SD)	Mean difference	Mean difference	*p* = 0.XX
Indirect costs (3 months)	Mean (SD)	Mean (SD)	Mean difference	Mean difference	*p* = 0.XX

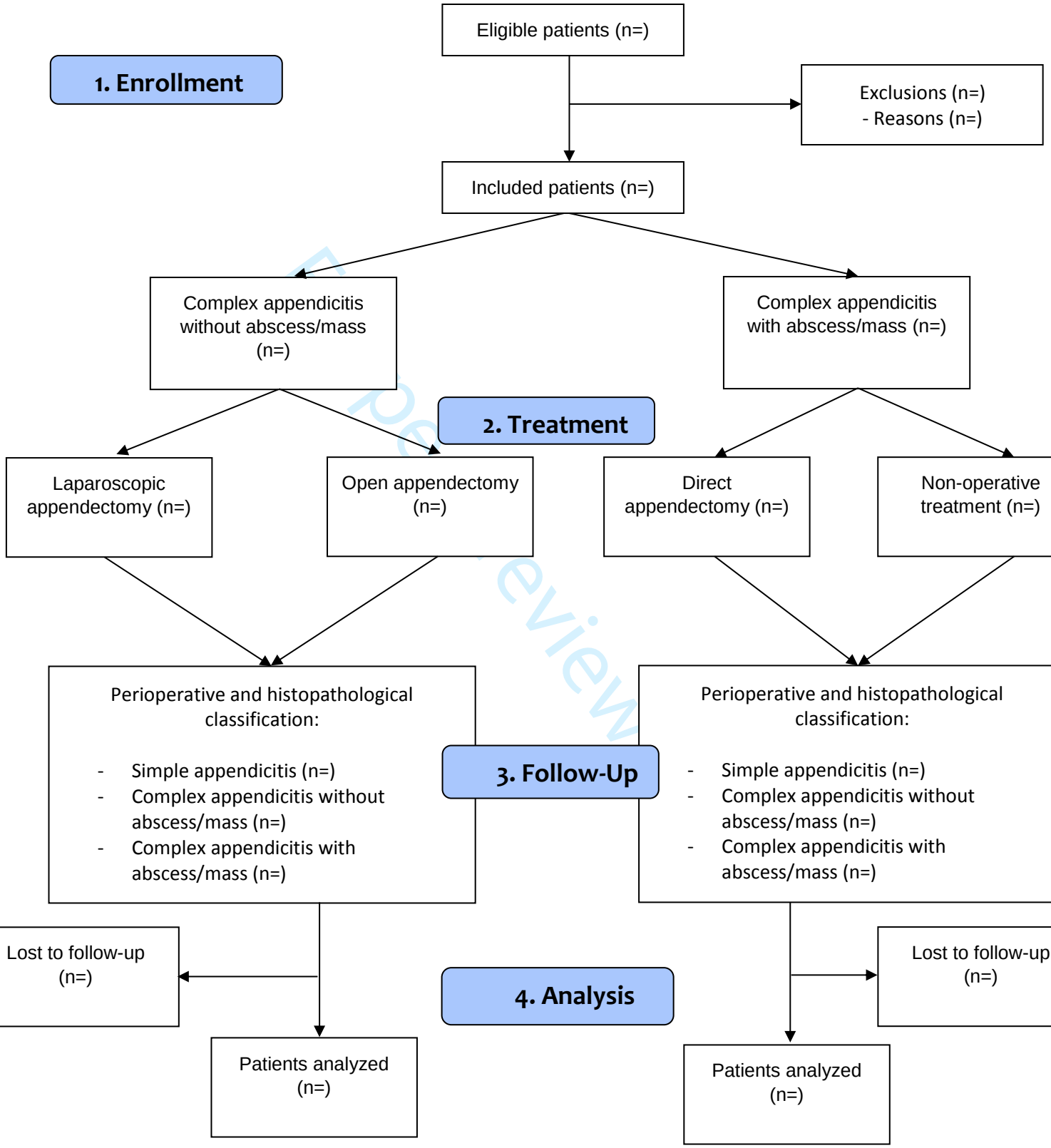
GP: General Practitioner; ED: Emergency Department; Hr-QoL: Health-related Quality of Life; PSQ: Patient Satisfaction Questionnaire
^ This column presents the pooled/combined results of the five propensity score strata

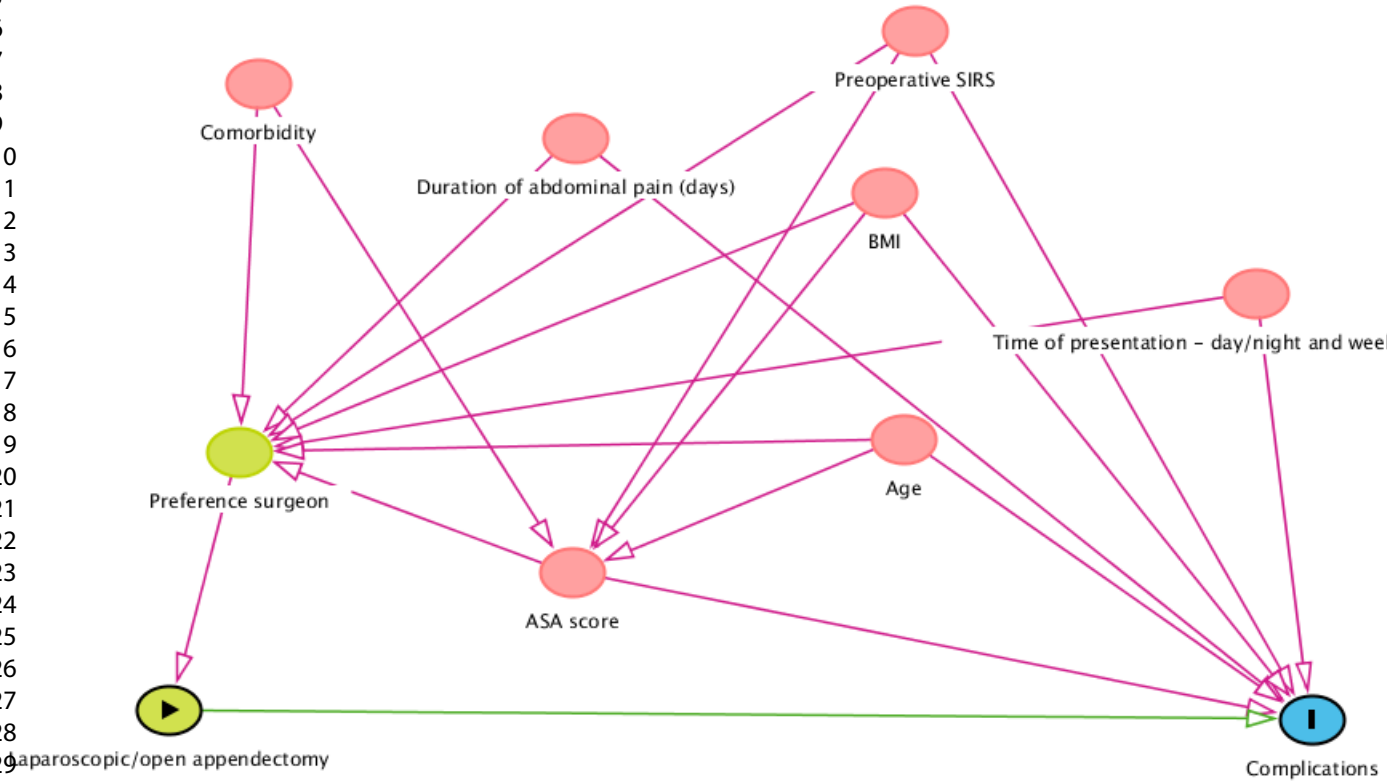
Table 6. Secondary outcomes subgroup 2

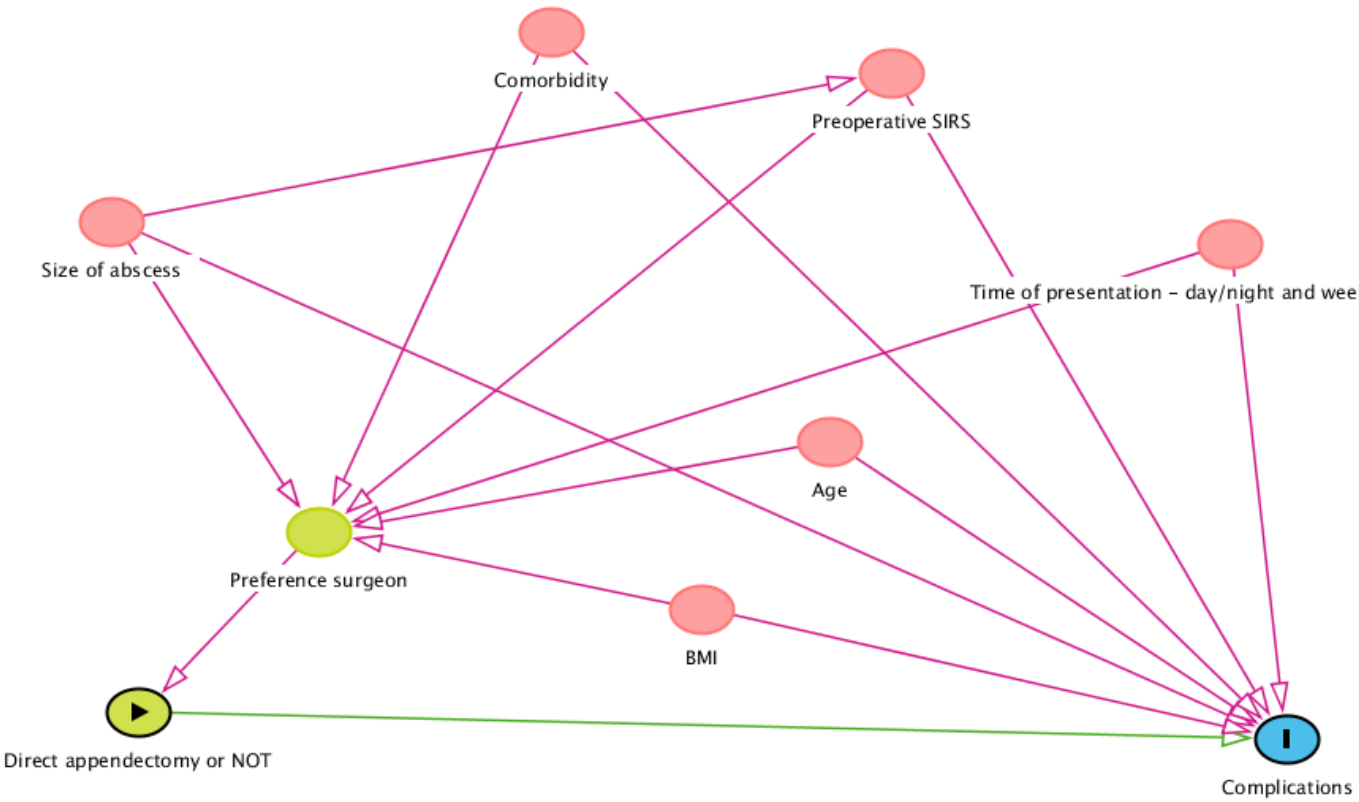
	Non-operative treatment, n	Direct appendectomy, n	Unadjusted Odds Ratio (OR)	Propensity score adjusted Odds Ratio	*p*-value
Any complication					
Admission, n (%)	N (% of Total)	N (% of Total)	OR (95%CI)	OR (95%CI)	*p* = 0.XX
30-days, n (%)	N (% of Total)	N (% of Total)	OR (95%CI)	OR (95%CI)	*p* = 0.XX
Intra-abdominal abscess (at 3 months), n (%)	N (% of Total)	N (% of Total)	OR (95%CI)	OR (95%CI)	*p* = 0.XX
Superficial Site Infection (at 3 months), n (%)	N (% of Total)	N (% of Total)	OR (95%CI)	OR (95%CI)	*p* = 0.XX
Secondary/prolonged bowel obstruction (at 3 months), n (%)	N (% of Total)	N (% of Total)	OR (95%CI)	OR (95%CI)	*p* = 0.XX
Length of hospital stay (days)	Mean (SD)	Mean (SD)	Mean difference	Mean difference	*p* = 0.XX
Level of pain (during admission)	Mean (SD)	Mean (SD)	Mean difference	Mean difference	*p* = 0.XX
Extra visits to GP, outpatient clinic or emergency department	Mean (SD)	Mean (SD)	Mean difference	Mean difference	*p* = 0.XX
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.XX
30 days	Mean (SD)	Mean (SD)			*p* = 0.XX
3 months	Mean (SD)	Mean (SD)			*p* = 0.XX
Patient Satisfaction (3 months)					
NET Promoter Score	Mean (SD)	Mean (SD)	Mean difference	Mean difference	*p* = 0.XX
PSQ-18	Mean (SD)	Mean (SD)			*p* = 0.XX
Direct costs (3 months)	Mean (SD)	Mean (SD)	Mean difference	Mean difference	*p* = 0.XX
Indirect costs (3 months)	Mean (SD)	Mean (SD)	Mean difference	Mean difference	*p* = 0.XX

GP: General Practitioner; ED: Emergency Department; Hr-QoL: Health-related Quality of Life; PSQ: Patient Satisfaction Questionnaire
^ This column presents the pooled/combined results of the five propensity score strata









Appendix 1. Standardized treatment strategies

Subgroup 1 (complex appendicitis without enlarged mass and or abscess formation):

Laparoscopic appendectomy:

Patients are admitted to the pediatric (surgical) ward and pain medication and intravenous fluids are administered according to the national guideline.[13] Antibiotic prophylaxis will be administered preoperatively consisting of a single dose (type of antibiotic according to local protocol). Laparoscopic appendectomy is performed according to daily practice but with the standardized key points as listed in box 1. Postoperative antibiotics are administered intravenously according to local protocol. If, after at least 48 hours of intravenous antibiotics, the patient is without fever for 24 hours, the decision can be made to change to oral antibiotics for a total length of five days. Discharge is allowed when the predefined discharge criteria have been met (Box 2).

Open appendectomy:

Pre- and postoperative care according to the same protocol as the laparoscopic appendectomy group. Open appendectomy is performed by a gridiron incision at McBurney's point and the appendiceal stump is closed by ligation.

Subgroup 2 (complex appendicitis with enlarged mass and or abscess formation):

Non-operative treatment:

Non-operative treatment consists of administration of intravenous antibiotics with or without drainage procedures (in case of abscess formation), reserving an appendectomy for those not responding or with recurrent disease. Antibiotic treatment consists of at least 48 hours of intravenous antibiotics. Proposed antibiotic regimens are a combination of amoxicillin/clavulanic acid 25/2.5mg/kg every six hours (maximum dose: 6000/600mg/day) and gentamicin (7mg/kg once daily) or a combination of intravenous cefuroxime 25mg/kg every six hours (maximum dose: 6000mg/day) and metronidazole 10mg/kg every eight hours

(maximum 4000mg/day). In case of an appendiceal abscess a drainage procedure can be performed either percutaneously or surgical. Prior to removal of the drainage tube imaging studies will be obtained to confirm complete resolution of the drained abscess.

Vital parameters are repeated every eight hours. Intravenous fluid is administered and pain medication prescribed according to the Dutch national guidelines.

If the patient has received 48 hours of intravenous antibiotics, a decrease in infection parameters is noted, and the patient is at least 24 hours without fever, the decision can be made to change to oral antibiotics with a total length of antibiotic treatment of five days.

In case of clinical deterioration, additional imaging studies, additional drainage procedures or an appendectomy can be performed at any time. This decision is left at the treating surgeon's discretion, but consultation with the study coordinators on the appropriate course of action is possible.

Discharge is allowed when the predefined discharge criteria have been met (Box 2).

Operative treatment:

Laparoscopic and open appendectomy are performed as described for patients in subgroup 1.

Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cohortreporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	1
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	3-5
Objectives	#3	State specific objectives, including any prespecified hypotheses	5
Methods			

Study design	#4	Present key elements of study design early in the paper	5
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	6
Eligibility criteria	#6b	For matched studies, give matching criteria and number of exposed and unexposed	n/a
Variables	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-11
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable.	8-11
Bias	#9	Describe any efforts to address potential sources of bias	11-13
Study size	#10	Explain how the study size was arrived at	7-8
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	11-13
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	11-13
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	11-13
Statistical methods	#12c	Explain how missing data were addressed	11-13
Statistical methods	#12d	If applicable, explain how loss to follow-up was addressed	11-13

Statistical methods	#12e	Describe any sensitivity analyses	
11-13			
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	Figure 2
Participants	#13b	Give reasons for non-participation at each stage	Figure 2
Participants	#13c	Consider use of a flow diagram	
Figure 2			
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	Table 1 / Table 2
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	
Table 1-6			
Descriptive data	#14c	Summarise follow-up time (eg, average and total amount)	
9			
Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	
Table 3-6			
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 3-6
Main results	#16b	Report category boundaries when continuous variables were categorized	n/a

Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
n/a			
Other analyses	#17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11-13, Table 3-6
Discussion			
Key results	#18	Summarise key results with reference to study objectives	n/a
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	15-22
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	15-22
Generalisability	#21	Discuss the generalisability (external validity) of the study results	15-22
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	28

Notes:

- 14a: Table 1 / Table 2
- 17: 11-13, Table 3-6 The STROBE checklist is distributed under the terms of the Creative Commons Attribution License CC-BY. This checklist was completed on 23. June 2021 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai