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| Complete List of Authors: | Knaapen, Max; Pediatric Surgical Center of Amsterdam; Emma Children's Hospital AMC and VU University Medical Center<br>van der Lee, Johanna H.; AMC, Pediatric Clinical Research Office<br>Bakx, Roel; Pediatric Surgical Center of Amsterdam; Emma Children's Hospital AMC and VU University Medical Center<br>The, Sarah-May; Pediatric Surgical Center of Amsterdam; Emma Children's Hospital AMC and VU University Medical Center<br>Van Heurn, Ernst; Pediatric Surgical Center of Amsterdam; Emma Children's Hospital AMC and VU University Medical Center<br>Heij, Hugo; Pediatric Surgical Center of Amsterdam; Emma Children's Hospital AMC and VU University Medical Center<br>Gorter, Ramon; Pediatric Surgical Center of Amsterdam; Emma Children's Hospital AMC and VU University Medical Center<br>., APAC collaborative study group |
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# Initial non-operative management of uncomplicated appendicitis in children: A protocol for a multicenter randomized controlled trial (APAC trial)

Knaapen M MD[1] van der Lee JH MD, PhD[2], Bakx R MD, PhD[1], The SML[1], van Heurn LWE MD. PhD[1], Heij HA MD, PhD[1], Gorter RR MD, PhD[1], APAC collaborative study group

1. Pediatric Surgical Center of Amsterdam; Emma Children's Hospital AMC and VU University Medical Center, Amsterdam, The Netherlands
2. Pediatric Clinical Research Office, Academic Medical Center, Amsterdam, The Netherlands

Address correspondence to M. Knaapen, MD
Address: Pediatric Surgical Center of Amsterdam; Emma Children's Hospital AMC, P.O. Box 22660, 1100 DD, Amsterdam, The Netherlands
Email: M.Knaapen@AMC.UvA.nl
Telephone: +31-20-444-2424
Fax: +31-20-444-2135

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## Abstract

### Introduction

Based on epidemiological, immunological and pathology data the idea that appendicitis is not necessarily a progressive disease is gaining ground. Two types are distinguished: simple and complicated appendicitis. Non-operative treatment (NOT) of children with simple appendicitis has been investigated in several small studies. So far it is deemed safe. However, its effectiveness and effect on quality of life (QoL) has yet to be established in a adequately powered randomized trial. In this article we provide the study protocol for the APAC trial.

### Methods and analysis

This multicenter, unblinded, non-inferiority, randomized controlled trial, randomizes children aged 7 to 17 years with imaging-confirmed simple appendicitis between appendectomy and NOT. Patients are recruited in 15 hospitals. The intended sample size, based on the primary outcome, rate of complications, is 334 patients.

NOT consists of IV antibiotics for 48-72 hours, daily blood tests, and ultrasound follow-up. If the patient meets the pre-defined discharge criteria, antibiotic treatment is continued orally at home. Primary outcome is the rate of complications at one year follow-up. An independent adjudication committee will assess all complications and their relation to the allocated treatment. Secondary outcomes include, but are not limited to, delayed appendectomies, QoL, pain, direct and indirect costs.

The primary outcome will be analysed both according to the intention-to-treat and to the per-protocol principle, and is presented with a one-sided 97.5% confidence interval. We will use multiple logistic and linear regression for binary and continuous outcomes, respectively, to adjust for stratification factors.

### Ethics and dissemination.

The protocol has been approved by the Medical Ethics Review Committee of the Academic Medical Center, Amsterdam. Data monitoring is performed by an independent institute and a Data Safety Monitoring Board has been assigned. Results will be presented in peer-reviewed academic journals and at (international) conferences.

### Registration details

NCT02848820; NTR5977

## Strengths and limitations of this study

1. Meticulous selection of children with uncomplicated appendicitis using strict (evidence based) criteria, including ultrasonography.
2. Elaborate follow-up on patient, parent, hospital and economic-level.
3. An independent adjudication committee assessing all complications and their relation to the allocated treatment.
4. The non-inferiority design does not allow for a superiority comparison of the rate of complications.

## Introduction

Appendicitis is a common gastro-intestinal disease with a lifetime incidence of 7-9%(1,2). Based on the assumption that urgent removal of the appendix is necessary to avoid progressive inflammation with subsequent necrosis and perforation of the appendix, emergency appendectomy has been the standard of care since 1889. However, based on epidemiological, immunological and pathology data, several experts have stated(3–6) that appendicitis is not necessarily a progressive disease. Rather, they endorse the idea that two types of appendicitis exist: simple or uncomplicated appendicitis and complicated appendicitis. Over the years, there has been a shift towards non-operative treatment strategies for diseases which were historically treated surgically, for instance, stomach ulcers and uncomplicated diverticulitis. More recently, non-operative treatment (NOT) of acute uncomplicated appendicitis (AUA) has become the subject of investigation. This strategy consists of initial treatment with intravenous antibiotics and reserves appendectomy for non-responders and those with recurrent appendicitis.

Several randomized controlled trials (RCTs) looked at the non-operative treatment of AUA in the adult population. Results, however, vary. Most trials conclude that NOT is safe, but the reported reduction of complications varies from no significant differences(7,8) to up to 39% reduction(9). Recurrent symptoms resulting in delayed appendectomy occur in roughly 1 in 4 patients(7–9). These numbers are interpreted in different ways, as is illustrated by the conclusions of three recent systematic reviews, which range from indicating NOT as the preferred treatment(9) to rejecting it as a routine treatment due to insufficient knowledge about its impact on quality of life (QoL)(8).

One third of all cases of appendicitis occur under the age of 20 years. The relevance of NOT in children might even be greater than in the adult population, since In children aged 5 to 18 years 68-90% of all cases of appendicitis are uncomplicated(2,10), which is high compared to the adult population. However, data in the pediatric population on the outcome of NOT for uncomplicated appendicitis is scarce and consists mainly of uncontrolled studies with small patient numbers. Recently a systematic review was published, including 10 studies (1 pilot RCT, 6 prospective cohorts and 3 retrospective cohorts) with a total of 413 children treated with NOT(11). Overall complications where reported in 5 of the 6 comparative studies. One out of 175 (0.6%) patients in the NOT group suffered complications vs. 9/239 (3.8%) patients in the primary appendectomy group. Follow-up ranged from 8 weeks to 4 years, with 82% of the NOT patients not having undergone appendectomy at follow-up completion. Recurrent appendicitis occurred in 68/396 (17%) patients; this included 19 children who were treated with a second course of antibiotics.

The evidence regarding the outcome of NOT in the pediatric population is far from sufficient. As of today, apart from the trial described in this article, four large RCTs(12–15) are recruiting children for

a comparison of primary appendectomy with NOT. In the Antibiotics versus Primary Appendectomy in Children (APAC) trial we aim to evaluate the effectiveness of the initial NOT strategy (reserving appendectomy for those not responding or with recurrent disease) compared to immediate appendectomy in terms of complications, health-related QoL and costs in children aged 7 to 17 years with AUA.

## Methods and analysis

### *Study design*

The APAC trial is a multicenter non-inferiority randomized controlled trial. Blinding was not deemed feasible. The protocol was drafted in accordance with the SPIRIT statements (Standard Protocol Items: Recommendations for Interventional Trials)(16). This trial was registered at clinicaltrials.gov (NCT02848820) and the Dutch Trial Registry (NTR5977) prior to the start of inclusion.

### *Patient selection*

Eligible for inclusion are children 7 to 17 years old of both sexes, in whom a imaging-confirmed acute uncomplicated appendicitis is diagnosed in the emergency department of one of the participating hospitals.

*Inclusion criteria*

Definition of AUA is based upon the following criteria.

- Clinical & biochemical criteria:
  - Localized tenderness in the right iliac fossa region
  - Normal/hyperactive bowel sounds
  - No guarding or palpable mass
  - Biochemical signs of infection:
    - Elevated white blood cell count (WBC)
    - Elevated C-reactive protein (CRP)

- Ultrasound criteria to confirm the diagnosis of AUA:
  - A non-compressible, painful appendix with an outer diameter > 6 mm
  - Secondary signs of inflammation, i.e. infiltration of the surrounding fat
  - Hyperemia within the appendiceal wall

In case the ultrasound is inconclusive, additional imaging (MRI or CAT-scan) may be obtained.

*Exclusion criteria*

- Generalized peritonitis or sepsis (as defined by the international pediatric sepsis consensus conference(17))
- Findings on imaging indicative of complex appendicitis:
  - significant and/or unclear free fluid
  - signs of perforation
  - signs of intra-abdominal abscess or phlegmone
- Faecolith, which might be associated with a higher risk of NOT failure(18–20)
- Serious co-morbidity such as cardiac or pulmonary disease with significant hemodynamic consequences, immunodeficiency, malignancy or sickle cell disease

- A history of non-operatively treated appendicitis
- Suspicion of an underlying malignancy or inflammatory bowel disease
- Documented type 1 allergy to the antibiotics used
- A complex appendicitis risk score indicative of complex appendicitis

*Complex appendicitis risk score*

A pediatric scoring system is used(21) predicting the risk of having complex appendicitis based upon five pre-operative variables; abdominal guarding, signs of complex appendicitis on ultrasound, CRP level, temperature and days of abdominal pain. In an independent validation in a second pediatric cohort a score below 4 had a negative predictive value of 98% (95% confidence interval(CI) 88-100). Children presenting with a score of 4 or higher will be excluded from this study because of the risk of having complicated appendicitis.

***Randomization***

After written informed consent from parents and child (assent from children under the age of 12) patients are randomized using the web-based randomization program Castor Electronic Data Capture version 4.10(22), stratified by center. A variable block algorithm is used to ensure concealment of allocation.

***Sample size calculation***

A non-inferiority design is used based upon evidence in the literature that NOT has potential secondary advantages. It would be sufficient when this trial demonstrates that the outcome in terms of complications is not worse in the NOT group as compared to the immediate appendectomy group. The overall frequency of post-operative complications after appendectomy is approximately 10%, meaning that 90% will be successfully treated without complications. If the difference in complication rate is less than 5%, non-inferiority is assumed. Using a 1-sided alpha of 2.5%, circa 150 patients per group are needed to achieve 90% power for the exclusion of a difference in favor of the usual care group of more than 5%. Although in our pilot study(23) the drop-out rate in one year was only 2%, we take into account a drop-out rate of 10%. Therefore, the number of patients to be included is 334.

***Study setting and feasibility***

Eligible patients are recruited in 15 hospitals across the Netherlands. This selection consists of both academic and large teaching hospitals. Inclusion started in January 2017. Based on data supplied by the participating hospitals approximately 225 children per year will meet the inclusion criteria. In our pilot study 57% of eligible patients participated. Taking these numbers into account we expect to include 128 patients per year. We therefore expect to complete inclusion within 32 months. All of the clinical, biochemical and imaging assessments are part of the standard work-up for children suspected of having appendicitis in the Netherlands, as described in the Dutch national guideline(24).

***Interventions***

*Non-operative management*

Antibiotic treatment consists of 48 hours of intravenous (IV) amoxicillin/clavulanic acid 25/2.5 mg/kg 6-hourly (maximum dose: 6000/600 mg per day) and gentamicin (7 mg/kg once daily). When the patient meets the pre-defined discharge criteria after 48 hours (Table 1) he/she is discharged with

oral antibiotics. If not, IV antibiotics are continued with a maximum total duration of 72 hours. Oral treatment consists of amoxicillin/clavulanic acid 50/12.5 mg/kg in three daily doses (maximum dose: 1500/375 mg per day). Total duration of antibiotic treatment is 7 days.

| **Pre-defined discharge criteria (equal for both interventions)** | |
|---|---|
| 1. | Body temperature < 38.0 degrees Celsius |
| 2. | NRS <4 |
| 3. | Adequate oral intake |
| 4. | Able to mobilize |
| 5. | Consent of parents for discharge |
| **Pre-defined discharge only for non-operative management** | |
| 6. | Decreased leukocytosis |
| 7. | Decreased C-reactive protein |
| 8. | No signs of complex appendicitis on 2$^{nd}$ ultrasound |

**Table 1. Pre-defined discharge criteria. All criteria have to be met to allow patient to be discharged**

To optimize early detection of NOT failure, WBC and CRP are measured every 24 hours during the time of administration of IV antibiotics. After 48 hours the abdominal ultrasound is repeated to check for signs of complicated appendicitis. Pre-defined criteria of clinical deterioration (Figure 1) define the indication for appendectomy.

A physician reassesses the patient twice daily. Vital parameters including Numeric Rating Scale (NRS) pain scores are repeated every 6 hours. IV fluid administration is protocolized and weight adjusted, with no oral intake during the first 12 hours. Pain medication is prescribed according to the national guideline(25).

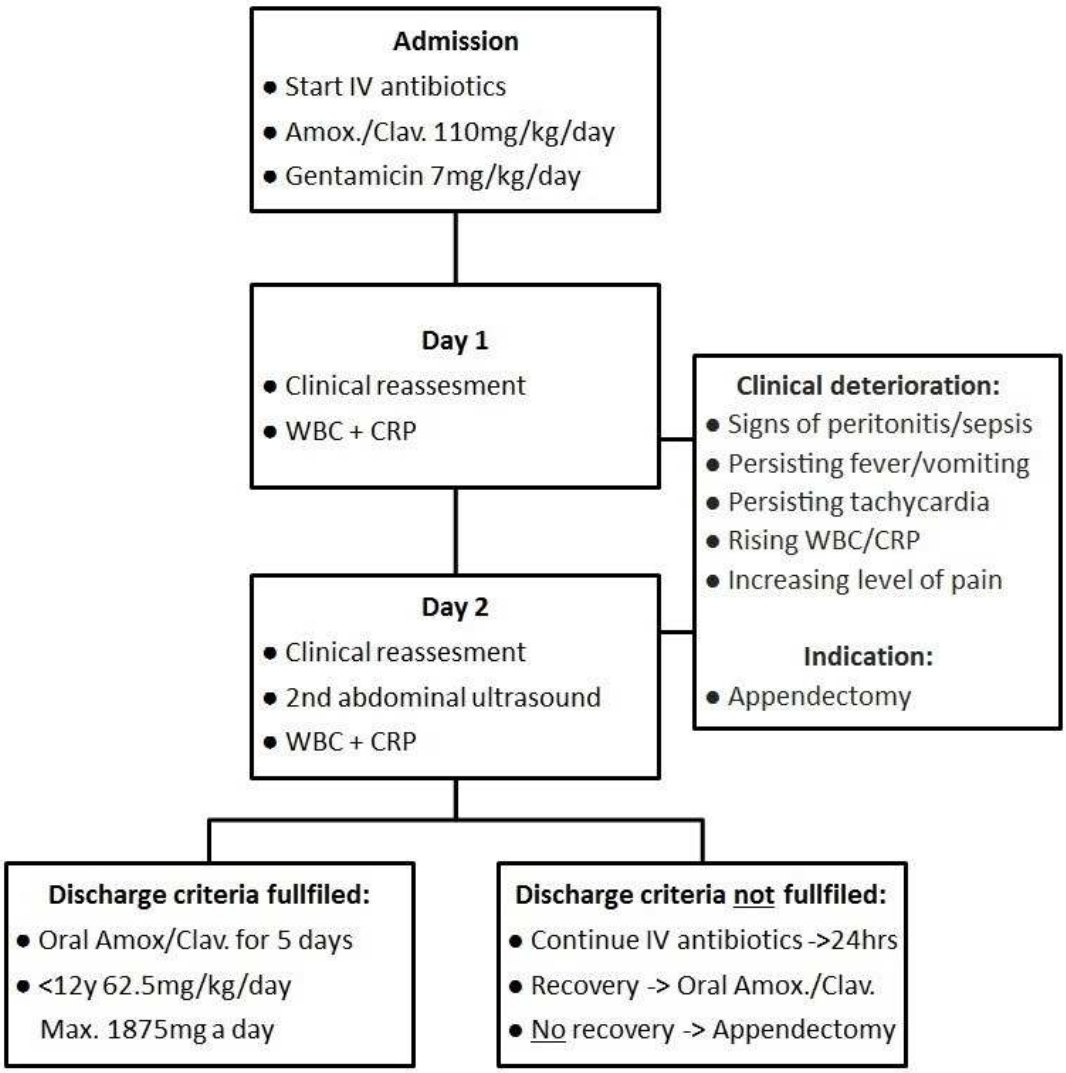


**Figure 1. Flowchart non-operative management**

*Operative management*

IV fluids and pain medication is administered according to the same protocol as the NOT group. Antibiotic prophylaxis, operative approach and post-operative care are all according to local protocol. Post-operative antibiotics are only warranted in the event of an unexpected complex appendicitis. Discharge is allowed when the predefined discharge criteria have been met (Table 1).

## Outcome and statistical analysis

***Primary outcome***

The primary outcome is defined as the complication rate at one year follow-up. An independent adjudication committee will review all complications and adverse events to assess their relation to the allocated treatment. Delayed appendectomy is not considered a complication, as we consider appendectomy necessary in patients who do not respond to initial non-operative management. However, we do report the rate of delayed appendectomies as a secondary outcome. Complications are defined as, but not limited to:

- Allergic reaction to antibiotics
- Need for surgical or radiological intervention other than appendectomy but related to appendicitis
- Re-admission for an indication other than recurrent appendicitis but related to the allocated treatment
- Complications associated with appendectomy:
    - Surgical site infection
    - Intra-abdominal abscess
    - Stump leakage/stump appendicitis
    - Secondary bowel obstruction, for instance as a result of adhesions
    - Anesthesia related complications, such as pneumonia
    - Hernia cicatricalis

***Secondary outcomes***

To evaluate the secondary endpoints follow-up will take place at 7 days, 4 weeks, 6 months and 1 year after randomization.

- Appendectomy related endpoints
    - Percentage of patients not having to undergo appendectomy
    - Percentage of patients with a missed diagnosis of complex appendicitis
    - Percentage of patients having to undergo appendectomy during initial antibiotic course
    - Patients with recurrent appendicitis within 1 year (histopathologically confirmed)
    - Percentage of patients undergoing interval appendectomy (histopathologically no sign of recurrent appendicitis)

- Patient related endpoints
    - Level of pain: assessed with by the NRS and total usage of pain medication on day 7
    - Health-related Quality of Life: assessed with the Child Health Questionnaire-Child Form 87 (CHQ-CF87)(26), the European Quality of Life-5Dimensions-Youth questionnaire (EQ-5D-Y) (child perspective) and European Quality of life-5Dimensions-Proxy questionnaire (EQ-5D-Proxy) (parent perspective)(27)
    - Patient satisfaction assessed with the NET promotor score and the validated Patient Satisfaction Questionnaire (PSQ-18)(28)
    - 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 to the outpatient clinic, general practitioner's office or emergency department for abdominal pain
    - Total length of hospital stay during the follow-up period for complications related to the allocated treatment

- Cost related endpoints
    - Non-medical and indirect costs at one year follow-up: using the Medical Consumption Questionnaire (iMCQ)(29) and the Productivity Cost Questionnaire (iPCQ)(30) adapted for use in children and parents

- Actual health care costs: variables gathered are, but not are limited to, number of follow-up out-patient clinic visits, number of general practitioner visits, number of emergency department visits and actual in-hospital generated costs

***Data analysis plan***

The primary analysis will be done according to the intention-to-treat (ITT) principle. A per-protocol analysis will be performed as well to prevent unjust rejection of the null hypothesis, which is a risk in non-inferiority research(31). We will use multiple logistic and linear regression analyses for binary and continuous outcomes, respectively, to adjust for stratification factors. Differences in proportions, numbers needed to treat and absolute and relative differences in continuous outcomes will be presented with the corresponding 95% CI, except for the percentage of patients with complications within one year (primary outcome), for which a one-sided 97.5% CI limit will be given in accordance with the non-inferiority design. In a secondary analysis the information recorded during the initial hospital stay will be analyzed using multiple logistic regression analysis in order to identify potential predictive variables for NOT failure. Statistical analyses will be performed using IBM SPSS Statistics Version 22.0 or higher (IBM Corp. released 2013. Armonk, NY).

## Ethics and dissemination.

***Data collection and confidentiality***

All data is handled confidentially and access is strictly limited in accordance with the Dutch Personal Data Protection Act. All participants are assigned a unique study code, which is not based on the patient initials or birth date. The master sheet only contains the study code and patient identification information. Data is gathered through clinical observations, outpatient clinic visits, follow-up phone calls and online questionnaires. All data is collected via Castor Electronic Data Capture(22), a web-based electronic case record form, which is built, maintained and has an audit trail all according to Good Clinical Practice guidelines. All data will be stored for a period of at least 15 years.

***Monitoring and safety***

Reliable high quality data is deemed of the upmost importance. The Clinical Research Bureau of the VU University Medical Centre will provide external monitoring, with monitoring visits of each participating center at least once a year.

The accredited Medical Ethics Review Committee of the Academic Medical Center, Amsterdam (MERC AMC) will be informed annually. All (serious) adverse events, suspected unexpected serious adverse reactions (SUSAR) and any other significant problems are reported to the MERC using an online submission system. To further assure the safety of participants an independent Data Safety Monitoring Board (DSMB) is installed, consisting of a surgeon, a pediatrician and a statistician. They receive an overview of the primary outcome six-monthly, as well as serious adverse events (SAEs), SUSARs and the number of patients having to undergo a delayed appendectomy. An interim analysis for efficacy will not be performed. If a serious concern arises for the safety of the patients in the trial, the DSMB can recommend early termination of the study. These agreements have been documented in a DSMB charter.

***Ethics***

The trial will be conducted in compliance with the current version of the Declaration of Helsinki, the ICH Good Clinical Practice guidelines E6(R1) and in accordance with the Dutch Medical Research Involving Human Subjects Act (WMO). The study protocol has been approved by the MREC AMC.

***Withdrawal***

Subjects can withdraw from the study without explanation at any time. They will be asked their reason for withdrawal, and they will be asked for permission to use their data. In case of withdrawal the patient will be treated according to the national protocol, which would be an appendectomy. However, the surgeon in charge of care can decide otherwise in agreement with the patient and his or her family. Patients can also be withdrawn by the surgeon or the investigator for urgent medical reasons.

***Dissemination plan***

Dispersion of the trial results will be accomplished by publication in an international peer-reviewed scientific journal and by presentations at (international) conferences. When the results of the trial warrant changes in the standard treatment guidelines of simple appendicitis, we reckon that the widespread execution of the trial in centers throughout the Netherlands will aid in its implementation.

*Implementation study*

To ensure optimal implementation a problem analysis will be conducted parallel to this RCT, investigating the promoting and obstructing determinants of implementation from patients', surgeons', organizational and social-political perspective. This qualitative study will include structured interviews with patients, parents, professionals and other stakeholders.

## Discussion

*Strengths and limitations of this study*

This trial only includes patients with imaging-confirmed appendicitis, thus reducing the risk of including patients with other diagnoses, or those with a non-inflamed appendix. Since the implementation of a guideline in the Netherlands promoting pre-operative imaging, the per-operative finding of non-inflamed appendices was reduced to 3.3%(32), which is low compared to for example the UK, where it is 20.6%(33). We postulate that our use of elaborate and, where possible, evidence-based patient selection methods enhances the chance of successful non-operative management. To warrant the safety of patients undergoing NOT, this protocol dictates systematic and frequent evaluation (by clinical assessment, laboratory tests and imaging studies). We expect this will identify patients not responding to the antibiotic treatment at an early stage.

The non-inferiority design does not allow for a superiority comparison for the rate of complications. The design choice was based on the argument that both treatment strategies are 100% effective in treating appendicitis, because when antibiotic treatment is not successful and when recurrent appendicitis occurs, appendectomy is performed. We postulate that the non-operatively treated patients who do not require appendectomy will have a reduction in costs, better quality of life and the avoidance of the complications associated with appendectomy. Essential for the possible acceptance of this new strategy is that it is not inferior when it comes to the risk of complications. To

determine the severity of possible complications and their relation with the allocated treatment we consider the support of an independent adjudication committee a great asset.

The inclusion and exclusion criteria of this trial are mostly based on data that allow for distinguishing complex from uncomplicated appendicitis. Criteria that predict the risk of NOT failure would be more adequate. However, more data and more experience are needed to be able to develop such criteria. Data from the APAC trial will also be used to analyze predictors of failure.

*Complicated appendicitis*

Reluctance of some surgeons towards NOT might be explained by the fear of missing complicated appendicitis and delaying appropriate treatment. In 4.5-6.5% of the adult population treated with NOT who underwent delayed appendectomy, complicated appendicitis was found(7,9). The outcome in terms of post-appendectomy complications after delayed appendectomy (6.9%) is comparable to that for primary appendectomy (8.8%)(8).

*Follow-up/long-term effects*

Information regarding long-term results of NOT in simple appendicitis is limited and it is scarce in children. One study in children with an average follow-up of 4.3 years reported that 22 of 78 (29%) children treated with NOT experienced recurrent appendicitis(19), with a median time to recurrence of 6 months. Eight percent of all non-operatively treated children experienced recurrence after more than 1 year. The APAC trial has a follow-up of 1 year. However, all participants who have not been operated at the end of the study will be asked to participate in long-term follow-up. The long-term effects in children of losing the function of the appendix have also not yet been cleared up. The appendix might play a role in immunity and there is evidence that it is involved in preserving a healthy gut microbiome(34).

*Choice of antibiotic regime*

Most of the data on antibiotic susceptibility in appendicitis is derived from studies in adults, patients with complicated appendicitis, and mixed patient groups. There is some evidence available concerning children. A study analyzing cultures from children in Ireland with complicated appendicitis revealed that the combination therapy of amoxicillin-clavulanic acid and aminoglycosides would be appropriate in 99% of children with bacterial appendicitis-related peritonitis(35). Since antibiotic resistance rates are greatly dependent on geography, we can expect comparable or even better results in the Netherlands, considering it has the lowest rates of antibiotic use in Europe(36). Combined with a low rate of complications and extensive experience with amoxicillin-clavulanic acid and gentamicin, we consider it the most sensible regime. Further research is carried out by our research group analyzing the microbiome in simple and complicated appendicitis. Hopefully this will contribute in determining the best antibiotic regime. If non-operative treatment of appendicitis is shown to be non-inferior in this trial, further research should determine the most sensible regime and treatment duration. The first pilot RCT evaluating outpatient conservative management in a mixed group (children and adults) has already been published(37).

*Antibiotic resistance*

A possible downside of NOT as opposed to surgery could be increased antibiotic resistance(38). Interestingly, a study evaluating bacterial resistance in complicated appendicitis in children showed no significant increase in resistance rates over the past 20 year(39). How this translates to bacterial resistance when simple appendicitis is treated with antibiotics, is unclear. The use of multi-drug

treatment regimens has been pointed out as one of the possibilities to reduce the development of resistant bacteria(40). Our choice for amoxicillin-clavulanic acid and gentamicin prevents us from having to use so-called reserve antibiotics, unlike most of the other know studies in children, in which for instance piperacillin-tazobactam is the drug of choice. Also when the symptoms do not resolve under the chosen antibiotic regimen, appendectomy is performed; we do not switch to other antibiotics.

*Value of histologic evaluation*

An occasionally mentioned argument(8) against non-operative treatment of appendicitis is the risk of missing other underlying causes of appendicitis, such as a carcinoid. One study repeated the abdominal ultrasound in children 1-3 months after NOT to ensure the diameter of the appendix returned to normal(19). The value of this strategy is unknown. In an analysis of 241 histopathologic appendectomy samples in children with simple appendicitis, 4 (1.6%) showed unexpected findings(41). Three parasitic infections and one Walthard cell rest were found; none of the findings required further treatment or investigation. The frequency of appendiceal carcinoid tumors in children undergoing appendectomy was 0.2%(42) and in less than 20% of these cases lymphovascular or mesenteric involvement was present. This seems a negligible risk and it is yet unclear if patients who are excluded or unresponsive to NOT are also the patients with the highest risk of having a malignancy as underlying cause.

## Footnotes

**Collaborators:** The surgical, pediatric, radiology, pharmacy and emergency medicine departments of the following Dutch hospitals contribute to the execution of this trial: Academic Medical Center, Amsterdam, The Netherlands; Ziekenhuis Amstelland, Amstelveen, The Netherlands; Catharina ziekenhuis, Eindhoven, The Netherlands; Elkerliek ziekenhuis, Helmond, The Netherlands; Erasmus Medical Center, Rotterdam, The Netherlands; Flevoziekenhuis, Almere, The Netherlands; Gelre Ziekenhuis, Apeldoorn, The Netherlands; Maxima Medical Center, Veldhoven, The Netherlands; Maastricht University Medical Center, Maastricht, The Netherlands; Noordwest Ziekenhuisgroep, Alkmaar, The Netherlands; OLVG, Amsterdam, The Netherlands; Rode Kruis Ziekenhuis, Beverwijk, The Netherlands; St. Antonius ziekenhuis, Nieuwegein, The Netherlands; University medical center Radboud, Nijmegen, The Netherlands; University Medical Center, Utrecht, The Netherlands; VU University Medical Center, Amsterdam, The Netherlands; Zuyderland, Heerlen/Sittard, The Netherlands.

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**Authors' contributions**: All authors have contributed to the design of this trial protocol. RRG, JHvdL and HAH were responsible for initiating the trial, with RB being the principal investigator. The protocol was drafted by RRG with contributions of JHvdL, SLT and HAH. Statistical advice was provided by JHvdL. MK was responsible for drafting the manuscript. All authors have contributed to the manuscript and read and approved the final manuscript.

**Data sharing statement:**
The trial is registered on ClinicalTrials.gov and the Dutch trial registry, both of which are open access. The study findings will be presented in a report which will be submitted for publication in a relevant peer-reviewed journal to ensure dissemination to relevant healthcare professionals. Findings may also be submitted for presentation at local meetings or conferences. The participant-level data set may be made available for meta-analyses pending relevant Medical Ethics Review Committee approval.

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**Competing interests statement:** None to declare

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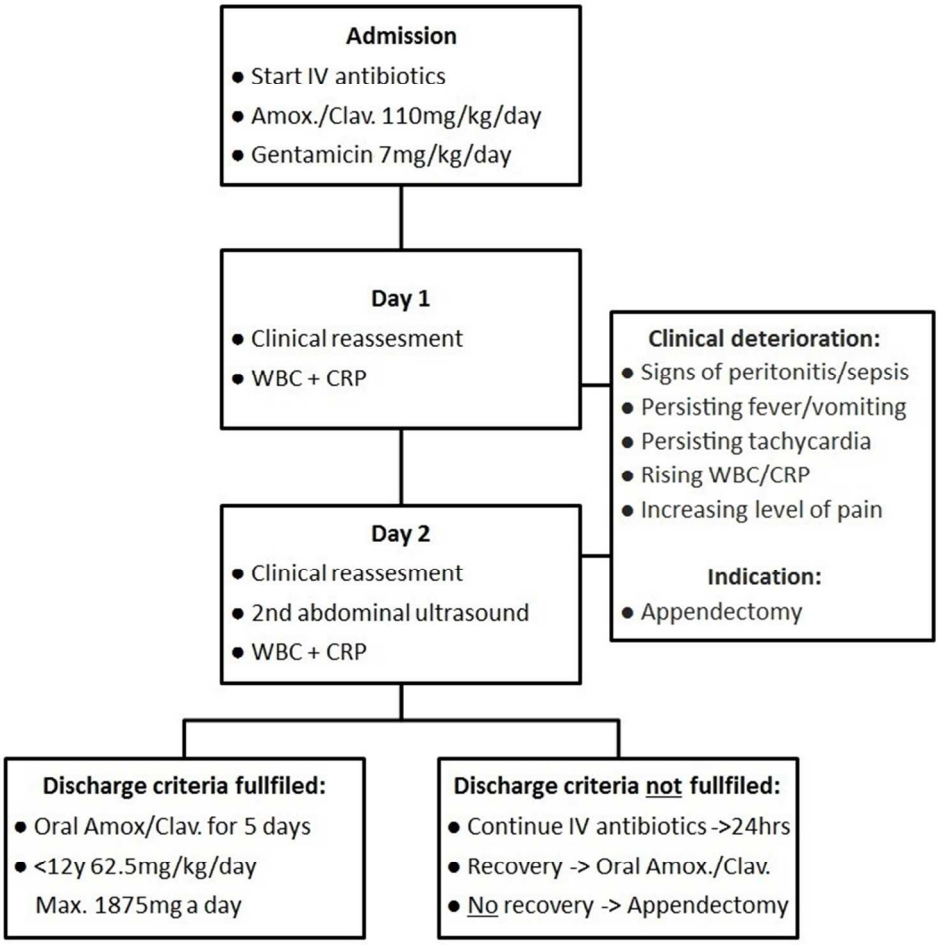


Figure 1. Flowchart non-operative management

212x205mm (96 x 96 DPI)


SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | Item No | Description | Addressed on page number |
|---|---|---|---|
| **Administrative information** | | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry | |
| | 2b | All items from the World Health Organization Trial Registration Data Set | |
| Protocol version | 3 | Date and version identifier | |
| Funding | 4 | Sources and types of financial, material, and other support | |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors | |
| | 5b | Name and contact information for the trial sponsor | |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | |
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | |

| | | | |
|---|---|---|---|
| **Introduction** | | | |
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention | |
| | 6b | Explanation for choice of comparators | |
| Objectives | 7 | Specific objectives or hypotheses | |
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) | |
| **Methods: Participants, interventions, and outcomes** | | | |
| Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained | |
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | |
| | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) | |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) | |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | |
| Outcomes | 12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | |
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | |

| | | | |
|---|---|---|---|
| Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | |

**Methods: Assignment of interventions (for controlled trials)**

| | | | |
|---|---|---|---|
| Allocation: | | | |
| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | |
| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | |
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | |

**Methods: Data collection, management, and analysis**

| | | | |
|---|---|---|---|
| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | |
| | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | |

| | | | |
|---|---|---|---|
| Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | |
| | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | |
| **Methods: Monitoring** | | | |
| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | |
| | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | |
| Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | |
| **Ethics and dissemination** | | | |
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | |
| Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) | |

| | | | |
|---|---|---|---|
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | |
| Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | |
| Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | |
| Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | |
| Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers | |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | |
| **Appendices** | | | |
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates | |
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | |

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. 

BMJ Open

# Initial non-operative management of uncomplicated appendicitis in children: A protocol for a multicenter randomized controlled trial (APAC trial)



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| | |

# Initial non-operative management of uncomplicated appendicitis in children: A protocol for a multicenter randomized controlled trial (APAC trial)

Knaapen M MD[1] van der Lee JH MD, PhD[2], Bakx R MD, PhD[1], The SML[1], van Heurn LWE MD. PhD[1], Heij HA MD, PhD[1], Gorter RR MD, PhD[1], APAC collaborative study group

1. Pediatric Surgical Center of Amsterdam; Emma Children's Hospital AMC and VU University Medical Center, Amsterdam, The Netherlands
2. Pediatric Clinical Research Office, Academic Medical Center, Amsterdam, The Netherlands

Address correspondence to M. Knaapen, MD
Address: Pediatric Surgical Center of Amsterdam; Emma Children's Hospital AMC, P.O. Box 22660, 1100 DD, Amsterdam, The Netherlands
Email: M.Knaapen@AMC.UvA.nl
Telephone: +31-20-444-2424
Fax: +31-20-444-2135

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Competing interests statement: None to declare

## Abstract

### Introduction

Based on epidemiological, immunological and pathology data the idea that appendicitis is not necessarily a progressive disease is gaining ground. Two types are distinguished: simple and complicated appendicitis. Non-operative treatment (NOT) of children with simple appendicitis has been investigated in several small studies. So far it is deemed safe. However, its effectiveness and effect on quality of life (QoL) has yet to be established in a adequately powered randomized trial. In this article we provide the study protocol for the APAC trial.

### Methods and analysis

This multicenter, non-inferiority, randomized controlled trial, randomizes children aged 7 to 17 years with imaging-confirmed simple appendicitis between appendectomy and NOT. Patients are recruited in 15 hospitals. The intended sample size, based on the primary outcome, rate of complications and a non-inferiority margin of 5%, is 334 patients.

NOT consists of IV antibiotics for 48-72 hours, daily blood tests, and ultrasound follow-up. If the patient meets the pre-defined discharge criteria, antibiotic treatment is continued orally at home. Primary outcome is the rate of complications at one year follow-up. An independent adjudication committee will assess all complications and their relation to the allocated treatment. Secondary outcomes include, but are not limited to, delayed appendectomies, QoL, pain, (in)direct costs.

The primary outcome will be analysed both according to the intention-to-treat and to the per-protocol principle, and is presented with a one-sided 97.5% confidence interval. We will use multiple logistic and linear regression for binary and continuous outcomes, respectively, to adjust for stratification factors.

### Ethics and dissemination.

The protocol has been approved by the Medical Ethics Review Committee of the Academic Medical Center, Amsterdam. Data monitoring is performed by an independent institute and a Data Safety Monitoring Board has been assigned. Results will be presented in peer-reviewed academic journals and at (international) conferences.

### Registration details

NCT02848820; NTR5977

## Strengths and limitations of this study

1. Meticulous selection of children with uncomplicated appendicitis using strict (evidence based) criteria, including ultrasonography.
2. Elaborate follow-up on patient, parent, hospital and economic-level.
3. An independent adjudication committee assessing all complications and their relation to the allocated treatment.
4. The non-inferiority design does not allow for a superiority comparison of the rate of complications.

## Introduction

Appendicitis is a common gastro-intestinal disease with a lifetime incidence of 7-9%(1,2). Based on the assumption that urgent removal of the appendix is necessary to avoid progressive inflammation with subsequent necrosis and perforation of the appendix, emergency appendectomy has been the standard of care since 1889. However, based on epidemiological, immunological and pathology data, several experts have stated(3–6) that appendicitis is not necessarily a progressive disease. Rather, they endorse the idea that two types of appendicitis exist: simple or uncomplicated appendicitis and complicated appendicitis. Over the years, there has been a shift towards non-operative treatment strategies for diseases which were historically treated surgically, for instance, stomach ulcers and uncomplicated diverticulitis. More recently, non-operative treatment (NOT) of acute uncomplicated appendicitis (AUA) has become the subject of investigation. This strategy consists of initial treatment with intravenous antibiotics and reserves appendectomy for non-responders and those with recurrent appendicitis.

Several randomized controlled trials (RCTs) looked at the non-operative treatment of AUA in the adult population. Results, however, vary. Most trials conclude that NOT is safe, but the reported reduction of complications varies from no significant differences(7,8) to up to 86% reduction(9). Recurrent symptoms resulting in delayed appendectomy occur in roughly 1 in 4 patients(7,8,10). These numbers are interpreted in different ways, as is illustrated by the conclusions of three recent systematic reviews, which range from indicating NOT as the preferred treatment(10) to rejecting it as a routine treatment due to insufficient knowledge about its impact on quality of life (QoL)(8).

Approximately one third of all cases of appendicitis occur under the age of 20 years. Regarding the distribution of uncomplicated and complicated appendicitis in the pediatric population, the percentage of uncomplicated appendicitis is reported to range between 68-90% in children aged 5 to 18 years(2,11). The percentage of complicated appendicitis increases with age(12), therefore reducing the amount of patients suitable for initial non-operative treatment strategy. Potential benefits of initial non-operative treatment strategy might therefore be higher for the pediatric population than for the adult population. Data in the pediatric population on the outcome of NOT for uncomplicated appendicitis is scarce and consists mainly of uncontrolled studies with small patient numbers. Recently a systematic review was published, including 10 studies (1 pilot RCT, 6 prospective cohorts and 3 retrospective cohorts) with a total of 413 children treated with NOT(13). Overall complications where reported in 5 of the 6 comparative studies. One out of 175 (0.6%) patients in the NOT group suffered complications vs. 9/239 (3.8%) patients in the primary appendectomy group. Follow-up ranged from 8 weeks to 4 years, with 82% of the NOT patients not having undergone appendectomy at follow-up completion. Recurrent appendicitis occurred in 68/396 (17%) patients; this included 19 children who were treated with a second course of antibiotics.

The evidence regarding the outcome of NOT in the pediatric population is far from sufficient. As of today, apart from the trial described in this article, four large clinical studies (three RCTs(14–16) and one prospective patient preference study(17)) are recruiting children for a comparison of primary appendectomy with NOT. In the Antibiotics versus Primary Appendectomy in Children (APAC) trial we aim to evaluate the effectiveness of the initial NOT strategy (reserving appendectomy for those not responding or with recurrent disease) compared to immediate appendectomy in terms of complications, health-related QoL and costs in children aged 7 to 17 years with AUA.

## Methods and analysis

***Study design***

The APAC trial is a multicenter non-inferiority randomized controlled trial. Blinding was not deemed feasible. The protocol was drafted in accordance with the SPIRIT statements (Standard Protocol Items: Recommendations for Interventional Trials)(18). This trial was registered at clinicaltrials.gov (NCT02848820) and the Dutch Trial Registry (NTR5977) prior to the start of inclusion.

***Patient selection***

Eligible for inclusion are children 7 to 17 years old of both sexes, in whom a imaging-confirmed acute uncomplicated appendicitis is diagnosed in the emergency department of one of the participating hospitals.

*Inclusion criteria*

Definition of AUA is based upon the following criteria.

- Clinical & biochemical criteria:
  - Localized tenderness in the right iliac fossa region
  - Normal/hyperactive bowel sounds
  - No guarding or palpable mass
  - Biochemical signs of infection:
    - Elevated white blood cell count (WBC)
    - Elevated C-reactive protein (CRP)

- Ultrasound criteria to confirm the diagnosis of AUA:
  - A non-compressible, painful appendix with an outer diameter > 6 mm
  - Secondary signs of inflammation, i.e. infiltration of the surrounding fat
  - Hyperemia within the appendiceal wall

In case the ultrasound is inconclusive, additional imaging (MRI or CAT-scan) may be obtained.

*Exclusion criteria*

- Generalized peritonitis or sepsis (as defined by the international pediatric sepsis consensus conference(19))
- Findings on imaging indicative of complex appendicitis:
  - significant and/or unclear free fluid
  - signs of perforation
  - signs of intra-abdominal abscess or phlegmone

- Children with a suspicion of an appendiceal faecalith on imaging studies are excluded, because of its association with a higher risk of NOT failure(20–23).
  Ultrasound characteristics for an appendicalith are defined as a echogenic, well-defined focus within the appendix with posterior acoustic shadowing.
- Serious co-morbidity such as cardiac or pulmonary disease with significant hemodynamic consequences, immunodeficiency, malignancy or sickle cell disease
- A history of non-operatively treated appendicitis
- Suspicion of an underlying malignancy or inflammatory bowel disease
- Documented type 1 allergy to the antibiotics used
- A complex appendicitis risk score indicative of complex appendicitis

*Complex appendicitis risk score*

A pediatric scoring system is used(24) predicting the risk of having complex appendicitis based upon five pre-operative variables; abdominal guarding, signs of complex appendicitis on ultrasound, CRP level, temperature and days of abdominal pain. In an independent validation in a second pediatric cohort a score below 4 had a negative predictive value of 98% (95% confidence interval(CI) 88-100%). Children presenting with a score of 4 or higher will be excluded from this study because of the risk of having complicated appendicitis.

***Randomization***

After written informed consent from parents and child (assent from children under the age of 12) patients are randomized using the web-based randomization program Castor Electronic Data Capture version 4.10(25), stratified by center. A variable block algorithm is used to ensure concealment of allocation.

***Sample size calculation***

A non-inferiority design is used based upon the notion that NOT potentially has secondary advantages, for instance cost reduction and less pain(26). We hypothesize that this might also be the case for QoL. It would thus be sufficient to demonstrate that the outcome in terms of complications is not worse in the NOT group compared to the immediate appendectomy group.
In our pilot study(27) we followed the children eligible for non-operative treatment who refused participation in that study and received immediate appendectomy instead of antibiotic treatment. The frequency of post-operative complications in this group at 1-year follow-up was approximately 10% (unpublished data), meaning that 90% was successfully treated without complications in the operative group. If the difference in complication rate between NOT and operative treatment is less than 5% in favour of appendectomy, non-inferiority is assumed. We will not be testing for the superiority of NOT. Using a 1-sided alpha of 2.5% in accordance with the non-inferiority design, 150 patients per group are needed to achieve 90% power for the exclusion of a difference in favour of the usual care group of more than 5%. Although in our pilot study(27) the drop-out rate after one year was only 2%, we take into account a drop-out rate of 10%. Therefore, the number of patients to be included is 334.

***Study setting and feasibility***

Eligible patients are recruited in 15 hospitals across the Netherlands. This selection consists of both academic and large teaching hospitals. Inclusion started in January 2017. Based on data supplied by

the participating hospitals approximately 225 children per year will meet the inclusion criteria. In our pilot study 57% of eligible patients participated. Taking these numbers into account we expect to include 128 patients per year. We therefore expect to complete inclusion within 32 months. All of the clinical, biochemical and imaging assessments are part of the standard work-up for children suspected of having appendicitis in the Netherlands, as described in the Dutch national guideline(28).

***Interventions***

*Non-operative management*

Antibiotic treatment consists of 48 hours of intravenous (IV) amoxicillin/clavulanic acid 25/2.5 mg/kg 6-hourly (maximum dose: 6000/600 mg per day) and gentamicin (7 mg/kg once daily). When the patient meets the pre-defined discharge criteria after 48 hours (Table 1) he/she is discharged with oral antibiotics. If not, IV antibiotics are continued with a maximum total duration of 72 hours. Oral treatment consists of amoxicillin/clavulanic acid 50/12.5 mg/kg in three daily doses (maximum dose: 1500/375 mg per day). Total duration of antibiotic treatment is 7 days.

| **Pre-defined discharge criteria (equal for both interventions)** | |
|---|---|
| 1. | Body temperature < 38.0 degrees Celsius |
| 2. | NRS <4 |
| 3. | Adequate oral intake |
| 4. | Able to mobilize |
| 5. | Consent of parents for discharge |
| **Pre-defined discharge only for non-operative management** | |
| 6. | Decreased leukocytosis |
| 7. | Decreased C-reactive protein |
| 8. | No signs of complex appendicitis on 2$^{nd}$ ultrasound |

**Table 1. Pre-defined discharge criteria. All criteria have to be met to allow patient to be discharged**

To optimize early detection of NOT failure, WBC and CRP are measured every 24 hours during the time of administration of IV antibiotics. After 48 hours the abdominal ultrasound is repeated to check for signs of complicated appendicitis. Pre-defined criteria of clinical deterioration (Figure 1) define the indication for appendectomy.

A physician reassesses the patient twice daily. Vital parameters including Numeric Rating Scale (NRS) pain scores are repeated every 6 hours. IV fluid administration is protocolized and weight adjusted, with no oral intake during the first 12 hours. Pain medication is prescribed according to the national guideline(29).

**Figure 1. Flowchart non-operative management**

*Operative management*

IV fluids and pain medication is administered according to the same protocol as the NOT group. Antibiotic prophylaxis, operative approach and post-operative care are all according to local protocol. Post-operative antibiotics are only warranted in the event of an unexpected complex appendicitis. Discharge is allowed when the predefined discharge criteria have been met (Table 1).

## Outcome and statistical analysis

***Primary outcome***

The primary outcome is defined as the complication rate at one year follow-up. An independent adjudication committee will review all complications and adverse events to assess their relation to the allocated treatment. The adjudication committee will categorize all complications using the Clavien-Dindo system(30). The Clavien-Dindo system was developed for reporting surgical complications. However, we expect that all possible complications of NOT can also be categorized within the same system, making a comparison between the two groups more consistent. We will report both the overall complication rate as well as subgroups based on complication severity. Any form of delayed appendectomy is not considered a complication, as we consider appendectomy necessary in patients who do not respond to initial non-operative management. This includes early failure during initial admission but also recurrent appendicitis after initial discharge. Complications as a result of a delayed appendectomy are included in the primary outcome.

Complications are defined as, but not limited to:

- Complications of antibiotic use: Allergic reaction with the need for treatment, gastro-intestinal symptoms with the need for treatment, secondary infections, etc.
- Need for surgical or radiological intervention other than appendectomy but related to appendicitis
- Re-admission for an indication other than recurrent appendicitis but related to the allocated treatment
- Complications associated with appendectomy:
    - Surgical site infection: Incisional and organ-space as defined by the CDC criteria(31). We do not differentiate between superficial and deep-incisional infection
    - Stump leakage/stump appendicitis in need of antibiotic treatment or surgical/radiological intervention
    - Secondary bowel obstruction confirmed by imaging or per-operative diagnosis with the need for (non-surgical) treatment. For instance as a result of adhesions
    - Anesthesia related complications, such as pneumonia (in need of antibiotic treatment)
    - Incisional hernia. Defined as any abdominal wall gap with or without a bulge in the area of a postoperative scar perceptible or palpable by clinical examination or imaging

***Secondary outcomes***

The rate of delayed appendectomy is reported as a secondary outcome. To evaluate the secondary endpoints follow-up will take place at 7 days, 4 weeks, 6 months and 1 year after randomization. Other secondary outcomes are listed below.

- Appendectomy related endpoints
    - Percentage of patients not having to undergo appendectomy
    - Percentage of patients with a missed diagnosis of complex appendicitis
    - Percentage of patients having to undergo appendectomy during initial antibiotic course

- Patients with recurrent appendicitis within 1 year (histopathologically confirmed)
- Percentage of patients undergoing interval appendectomy (histopathologically no sign of recurrent appendicitis)

- Patient related endpoints
  - Level of pain: assessed with by the NRS and total usage of pain medication on day 7
  - Health-related Quality of Life: assessed with the Child Health Questionnaire-Child Form 87 (CHQ-CF87)(32), the European Quality of Life-5Dimensions-Youth questionnaire (EQ-5D-Y) (child perspective) and European Quality of life-5Dimensions-Proxy questionnaire (EQ-5D-Proxy) (parent perspective)(33)
  - Patient satisfaction assessed with the NET promotor score and the validated Patient Satisfaction Questionnaire (PSQ-18)(34)
  - 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 to the outpatient clinic, general practitioner's office or emergency department for abdominal pain
  - Total length of hospital stay during the follow-up period, including admissions due to complications related to the allocated treatment. The length of initial hospital stay is included but will also be reported separately

- Cost related endpoints
  - Non-medical and indirect costs at one year follow-up: using the Medical Consumption Questionnaire (iMCQ)(35) and the Productivity Cost Questionnaire (iPCQ)(36) adapted for use in children and parents
  - Actual health care costs: variables gathered are, but not are limited to, number of follow-up out-patient clinic visits, number of general practitioner visits, number of emergency department visits and actual in-hospital generated costs

***Data analysis plan***

The primary analysis will be done according to the intention-to-treat (ITT) principle. A per-protocol analysis will be performed as well to prevent unjust rejection of the null hypothesis, which is a risk in non-inferiority research(37). We only consider cases as a treatment arm crossover if the randomly assigned treatment is switched because of patient and/or parental preference without their being medical grounds. Therefore patients receiving an appendectomy because of clinical deterioration, abdominal complaints after discharge, or recurrent appendicitis will be not be labeled as a crossover. We will use multiple logistic and linear regression analyses for binary and continuous outcomes, respectively, to adjust for stratification factors. Differences in proportions, numbers needed to treat and absolute and relative differences in continuous outcomes will be presented with the corresponding 95% CI, except for the percentage of patients with complications within one year (primary outcome), for which a one-sided 97.5% CI limit will be given in accordance with the non-inferiority design. In a secondary analysis the information recorded during the initial hospital stay will be analyzed using multiple logistic regression analysis in order to identify potential predictive variables for NOT failure. Statistical analyses will be performed using IBM SPSS Statistics Version 22.0 or higher (IBM Corp. released 2013. Armonk, NY).

## Ethics and dissemination.

***Data collection and confidentiality***

All data is handled confidentially and access is strictly limited in accordance with the Dutch Personal Data Protection Act. All participants are assigned a unique study code, which is not based on the patient initials or birth date. The master sheet only contains the study code and patient identification information. Data is gathered through clinical observations, outpatient clinic visits, follow-up phone calls and online questionnaires. All data is collected via Castor Electronic Data Capture(25), a web-based electronic case record form, which is built, maintained and has an audit trail all according to Good Clinical Practice guidelines. All data will be stored for a period of at least 15 years.

***Monitoring and safety***

Reliable high quality data is deemed of the upmost importance. The Clinical Research Bureau of the VU University Medical Centre will provide external monitoring, with monitoring visits of each participating center at least once a year.

The accredited Medical Ethics Review Committee of the Academic Medical Center, Amsterdam (MERC AMC) will be informed annually. All (serious) adverse events, suspected unexpected serious adverse reactions (SUSAR) and any other significant problems are reported to the MERC using an online submission system. To further assure the safety of participants an independent Data Safety Monitoring Board (DSMB) is installed, consisting of a surgeon, a pediatrician and a statistician. They receive an overview of the primary outcome six-monthly, as well as serious adverse events (SAEs), SUSARs and the number of patients having to undergo a delayed appendectomy. An interim analysis for efficacy will not be performed. If a serious concern arises for the safety of the patients in the trial, the DSMB can recommend early termination of the study. These agreements have been documented in a DSMB charter.

***Ethics***

The trial will be conducted in compliance with the current version of the Declaration of Helsinki, the ICH Good Clinical Practice guidelines E6(R1) and in accordance with the Dutch Medical Research Involving Human Subjects Act (WMO). The study protocol has been approved by the MREC AMC.

***Withdrawal***

Subjects can withdraw from the study without explanation at any time. They will be asked their reason for withdrawal, and they will be asked for permission to use their data. In case of withdrawal the patient will be treated according to the national protocol, which would be an appendectomy. However, the surgeon in charge of care can decide otherwise in agreement with the patient and his or her family. Patients can also be withdrawn by the surgeon or the investigator for urgent medical reasons.

***Dissemination plan***

Dispersion of the trial results will be accomplished by publication in an international peer-reviewed scientific journal and by presentations at (international) conferences. When the results of the trial warrant changes in the standard treatment guidelines of simple appendicitis, we reckon that the widespread execution of the trial in centers throughout the Netherlands will aid in its implementation.

*Implementation study*

To ensure optimal implementation a problem analysis will be conducted parallel to this RCT, investigating the promoting and obstructing determinants of implementation from patients', surgeons', organizational and social-political perspective. This qualitative study will include structured interviews with patients, parents, professionals and other stakeholders.

## Discussion

*Strengths and limitations of this study*

This trial only includes patients with imaging-confirmed appendicitis, thus reducing the risk of including patients with other diagnoses, or those with a non-inflamed appendix. Since the implementation of a guideline in the Netherlands promoting pre-operative imaging, the per-operative finding of non-inflamed appendices was reduced to 3.3%(38), which is low compared to for example the UK, where it is 20.6%(39). We postulate that our use of elaborate and, where possible, evidence-based patient selection methods enhances the chance of successful non-operative management. To warrant the safety of patients undergoing NOT, this protocol dictates systematic and frequent evaluation (by clinical assessment, laboratory tests and imaging studies). We expect this will identify patients not responding to the antibiotic treatment at an early stage.

The non-inferiority design does not allow for a superiority comparison for the rate of complications. The design choice was based on the argument that both treatment strategies are 100% effective in treating appendicitis, because when antibiotic treatment is not successful and when recurrent appendicitis occurs, appendectomy is performed. We postulate that the non-operatively treated patients who do not require appendectomy will have a reduction in costs, better quality of life and the avoidance of the complications associated with appendectomy. Essential for the possible acceptance of this new strategy is that it is not inferior when it comes to the risk of complications. To determine the severity of possible complications and their relation with the allocated treatment we consider the support of an independent adjudication committee a great asset.

The inclusion and exclusion criteria of this trial are mostly based on data that allow for distinguishing complex from uncomplicated appendicitis. Criteria that predict the risk of NOT failure would be more adequate. However, more data and more experience are needed to be able to develop such criteria. Data from the APAC trial will also be used to analyze predictors of failure.

*Choice of primary outcome*

Determining the appropriate primary outcome measure in studies comparing non-operative treatment to operative treatment remains challenging. In our opinion, both strategies will be effective in treating patients with appendicitis, and therefore effectiveness or failure is not an appropriate outcome measure. Therefore we decided to use a composite outcome measure i.e. complications. Such outcome measures (morbidity and mortality) are necessary in order to start the debate whether or not non-operative treatment strategy can be integrated in clinical practice. Furthermore our goal is to compare the initial non-operative treatment strategy (reserving an appendectomy for those not responding or with recurrent appendicitis) to direct operative treatment strategy. In this view, stating that delayed appendectomy for the indication of failed antibiotic treatment or recurrent appendicitis is a complication would not be appropriate as it is integrated in the treatment strategy. Post-operative complications after delayed appendectomy are however considered as complications of the initial non-operative treatment strategy. The amount of

delayed appendectomies (for both non-responders and recurrent appendicitis) needs be included in the debate whether or not initial non-operative treatment strategy can be implemented in daily practice. It is therefore reported as a secondary outcome.

*Complicated appendicitis*

Reluctance of some surgeons towards NOT might be explained by the fear of missing complicated appendicitis and delaying appropriate treatment. In 4.5-6.5% of the adult population treated with NOT who underwent delayed appendectomy, complicated appendicitis was found(7,10). The outcome in terms of post-appendectomy complications after delayed appendectomy (6.9%) is comparable to that for primary appendectomy (8.8%)(8).

*Exclusion of patients with appendiceal faecalith*

We excluded patients with a suspicion of an appendiceal faecalith on pre-operative imaging studies because it is associated with a higher failure rate of NOT. In the adult population a NOT failure rate after one month of 50% was reported in the group with a faecalith vs. 14% in the group without a faecalith(20). One study only including children with appendicitis and a faecalith on imaging had to terminate inclusions early because of a NOT failure rate of 60% at a median of 4.7 months follow-up (23). Faecaliths are also associated with a higher long term recurrence risk in children, with 47.4% recurrences vs 23.7% (21).

*Follow-up/long-term effects*

Information regarding long-term results of NOT in simple appendicitis is limited and it is scarce in children. One study in children with an average follow-up of 4.3 years reported that 22 of 78 (29%) children treated with NOT experienced recurrent appendicitis(21), with a median time to recurrence of 6 months. Eight percent of all non-operatively treated children experienced recurrence after more than 1 year. The APAC trial has a follow-up of 1 year. However, all participants who have not been operated at the end of the study will be asked to participate in long-term follow-up. The long-term effects in children of losing the function of the appendix have also not yet been cleared up. The appendix might play a role in immunity and there is evidence that it is involved in preserving a healthy gut microbiome(40).

*Choice of antibiotic regime*

Most of the data on antibiotic susceptibility in appendicitis is derived from studies in adults, patients with complicated appendicitis, and mixed patient groups. There is some evidence available concerning children. A study analyzing cultures from children in Ireland with complicated appendicitis revealed that the combination therapy of amoxicillin-clavulanic acid and aminoglycosides would be appropriate in 99% of children with bacterial appendicitis-related peritonitis(41). Since antibiotic resistance rates are greatly dependent on geography, we can expect comparable or even better results in the Netherlands, considering it has the lowest rates of antibiotic use in Europe(42). Combined with a low rate of complications and extensive experience with amoxicillin-clavulanic acid and gentamicin, we consider it the most sensible regime. Further research is carried out by our research group analyzing the microbiome in simple and complicated appendicitis. Hopefully this will contribute in determining the best antibiotic regime. If non-operative treatment of appendicitis is shown to be non-inferior in this trial, further research should determine the most sensible regime and treatment duration. The first pilot RCT evaluating outpatient conservative management in a mixed group (children and adults) has already been published(43).

*Antibiotic resistance*

A possible downside of NOT as opposed to surgery could be increased antibiotic resistance(44). Interestingly, a study evaluating bacterial resistance in complicated appendicitis in children showed no significant increase in resistance rates over the past 20 year(45). How this translates to bacterial resistance when simple appendicitis is treated with antibiotics, is unclear. The use of multi-drug treatment regimens has been pointed out as one of the possibilities to reduce the development of resistant bacteria(46). Our choice for amoxicillin-clavulanic acid and gentamicin prevents us from having to use so-called reserve antibiotics, unlike most of the other know studies in children, in which for instance piperacillin-tazobactam is the drug of choice. Also when the symptoms do not resolve under the chosen antibiotic regimen, appendectomy is performed; we do not switch to other antibiotics.

*Value of histologic evaluation*

An occasionally mentioned argument(8) against non-operative treatment of appendicitis is the risk of missing other underlying causes of appendicitis, such as a carcinoid. One study repeated the abdominal ultrasound in children 1-3 months after NOT to ensure the diameter of the appendix returned to normal(21). The value of this strategy is unknown. In an analysis of 241 histopathologic appendectomy samples in children with simple appendicitis, 4 (1.6%) showed unexpected findings(47). Three parasitic infections and one Walthard cell rest were found; none of the findings required further treatment or investigation. The frequency of appendiceal carcinoid tumors in children undergoing appendectomy was 0.2%(48) and in less than 20% of these cases lymphovascular or mesenteric involvement was present. This seems a negligible risk and it is yet unclear if patients who are excluded or unresponsive to NOT are also the patients with the highest risk of having a malignancy as underlying cause.

Unique for the APAC trial is its primary outcome measure; total number of complications after 1 year. Delayed appendectomy or recurrence is not reported as the primary endpoint or as a complication. Because in our opinion there is a place for the appendectomy in non-operative management as a step-up approach for children unresponsive to antibiotic treatment. As a result eight or nine out of every 10 children with uncomplicated appendicitis would no longer have to undergo an appendectomy. Furthermore if we are able to identify specific predictive pre-operative variables, we might identify a group of patients with even better (long-term) outcomes. Finally this trial should answer the question whether the advantages of NOT are also reflected in the reported quality of life and diminished costs.

## Footnotes

**Collaborators:** The surgical, pediatric, radiology, pharmacy and emergency medicine departments of the following Dutch hospitals contribute to the execution of this trial: Academic Medical Center, Amsterdam, The Netherlands; Ziekenhuis Amstelland, Amstelveen, The Netherlands; Catharina ziekenhuis, Eindhoven, The Netherlands; Elkerliek ziekenhuis, Helmond, The Netherlands; Erasmus Medical Center, Rotterdam, The Netherlands; Flevoziekenhuis, Almere, The Netherlands; Gelre Ziekenhuis, Apeldoorn, The Netherlands; Maxima Medical Center, Veldhoven, The Netherlands; Maastricht University Medical Center, Maastricht, The Netherlands; Noordwest Ziekenhuisgroep, Alkmaar, The Netherlands; OLVG, Amsterdam, The Netherlands; Rode Kruis Ziekenhuis, Beverwijk, The Netherlands; St. Antonius ziekenhuis, Nieuwegein, The Netherlands; University medical center Radboud, Nijmegen, The Netherlands; University Medical Center, Utrecht, The Netherlands; VU University Medical Center, Amsterdam, The Netherlands; Zuyderland, Heerlen/Sittard, The Netherlands.

**Acknowledgments**
Due to the multi-center and multidisciplinary nature of the trial not all supporting researchers can be mentioned by name. However we would like to acknowledge all supporting pediatricians, radiologists, pharmacists, emergency medicine physicians and pediatric nurses. And we would like to thank all of the supporting staff and other physicians that make the realization of this trial possible. We would also like to acknowledge the Dutch Foundation Children and Hospital for their advice and support in drafting the protocol.

**Authors' contributions**: All authors have contributed to the design of this trial protocol. RRG, JHvdL and HAH have initiated the project. LWEvH and RB are the chief investigators. The protocol was drafted by RRG which was refined by JHvdL, SMLT, LWEvH, RB and HAH. Statistical advice was provided by JHvdL. MK was responsible for drafting this manuscript. All authors have contributed to the manuscript and read and approved the final manuscript..

**Data sharing statement:**
The trial is registered on ClinicalTrials.gov and the Dutch trial registry, both of which are open access. The study findings will be presented in a report which will be submitted for publication in a relevant peer-reviewed journal to ensure dissemination to relevant healthcare professionals. Findings may also be submitted for presentation at local meetings or conferences. The participant-level data set may be made available for meta-analyses pending relevant Medical Ethics Review Committee approval.

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**Competing interests statement:** None to declare

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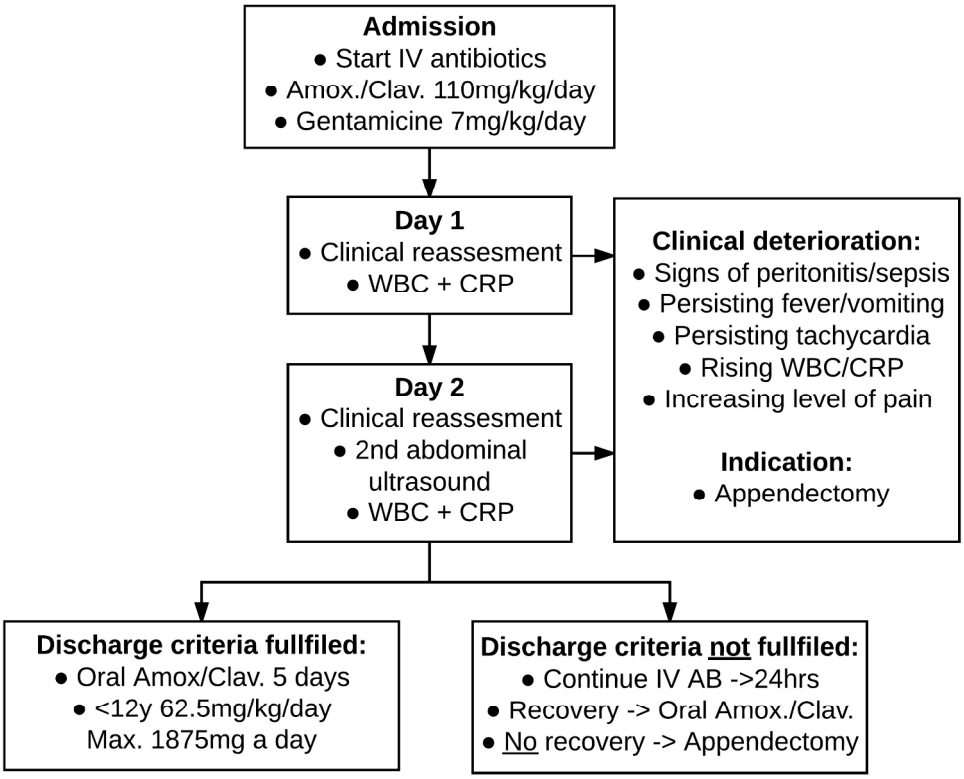


Figure 1. Flowchart non-operative management

217x178mm (300 x 300 DPI)


SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | Item No | Description | Addressed on page number |
|---|---|---|---|
| **Administrative information** | | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry | |
| | 2b | All items from the World Health Organization Trial Registration Data Set | |
| Protocol version | 3 | Date and version identifier | |
| Funding | 4 | Sources and types of financial, material, and other support | |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors | |
| | 5b | Name and contact information for the trial sponsor | |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | |
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | |

**Introduction**

| | | | |
|---|---|---|---|
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention | |
| | 6b | Explanation for choice of comparators | |
| Objectives | 7 | Specific objectives or hypotheses | |
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) | |

**Methods: Participants, interventions, and outcomes**

| | | | |
|---|---|---|---|
| Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained | |
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | |
| | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) | |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) | |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | |
| Outcomes | 12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | |
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | |

| | | | |
|---|---|---|---|
| Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | |

**Methods: Assignment of interventions (for controlled trials)**

| | | | |
|---|---|---|---|
| Allocation: | | | |
| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | |
| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | |
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | |

**Methods: Data collection, management, and analysis**

| | | | |
|---|---|---|---|
| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | |
| | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | |

| | | | |
|---|---|---|---|
| Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | |
| | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | |
| **Methods: Monitoring** | | | |
| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | |
| | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | |
| Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | |
| **Ethics and dissemination** | | | |
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | |
| Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) | |

| | | | |
|---|---|---|---|
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | |
| Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | |
| Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | |
| Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | |
| Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers | |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | |
| **Appendices** | | | |
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates | |
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | |

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. 

BMJ Open

# Initial non-operative management of uncomplicated appendicitis in children: A protocol for a multicenter randomized controlled trial (APAC trial)



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| | |

# Initial non-operative management of uncomplicated appendicitis in children: A protocol for a multicenter randomized controlled trial (APAC trial)

Knaapen M MD[1] van der Lee JH MD, PhD[2], Bakx R MD, PhD[1], The SML[1], van Heurn LWE MD. PhD[1], Heij HA MD, PhD[1], Gorter RR MD, PhD[1], APAC collaborative study group

1. Pediatric Surgical Center of Amsterdam; Emma Children's Hospital AMC and VU University Medical Center, Amsterdam, The Netherlands
2. Pediatric Clinical Research Office, Academic Medical Center, Amsterdam, The Netherlands

Address correspondence to M. Knaapen, MD
Address: Pediatric Surgical Center of Amsterdam; Emma Children's Hospital AMC, P.O. Box 22660, 1100 DD, Amsterdam, The Netherlands
Email: M.Knaapen@AMC.UvA.nl
Telephone: +31-20-444-2424
Fax: +31-20-444-2135

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## Abstract

### Introduction

Based on epidemiological, immunological and pathology data the idea that appendicitis is not necessarily a progressive disease is gaining ground. Two types are distinguished: simple and complicated appendicitis. Non-operative treatment (NOT) of children with simple appendicitis has been investigated in several small studies. So far it is deemed safe. However, its effectiveness and effect on quality of life (QoL) has yet to be established in a adequately powered randomized trial. In this article we provide the study protocol for the APAC trial.

### Methods and analysis

This multicenter, non-inferiority, randomized controlled trial, randomizes children aged 7 to 17 years with imaging-confirmed simple appendicitis between appendectomy and NOT. Patients are recruited in 15 hospitals. The intended sample size, based on the primary outcome, rate of complications and a non-inferiority margin of 5%, is 334 patients.

NOT consists of IV antibiotics for 48-72 hours, daily blood tests, and ultrasound follow-up. If the patient meets the pre-defined discharge criteria, antibiotic treatment is continued orally at home. Primary outcome is the rate of complications at one year follow-up. An independent adjudication committee will assess all complications and their relation to the allocated treatment. Secondary outcomes include, but are not limited to, delayed appendectomies, QoL, pain, (in)direct costs.

The primary outcome will be analysed both according to the intention-to-treat and to the per-protocol principle, and is presented with a one-sided 97.5% confidence interval. We will use multiple logistic and linear regression for binary and continuous outcomes, respectively, to adjust for stratification factors.

### Ethics and dissemination.

The protocol has been approved by the Medical Ethics Review Committee of the Academic Medical Center, Amsterdam. Data monitoring is performed by an independent institute and a Data Safety Monitoring Board has been assigned. Results will be presented in peer-reviewed academic journals and at (international) conferences.

### Registration details

NCT02848820; NTR5977

## Strengths and limitations of this study

1. Meticulous selection of children with uncomplicated appendicitis using strict (evidence based) criteria, including ultrasonography.
2. Elaborate follow-up on patient, parent, hospital and economic-level.
3. An independent adjudication committee assessing all complications and their relation to the allocated treatment.
4. The non-inferiority design does not allow for a superiority comparison of the rate of complications.

## Introduction

Appendicitis is a common gastro-intestinal disease with a lifetime incidence of 7-9%(1,2). Based on the assumption that urgent removal of the appendix is necessary to avoid progressive inflammation with subsequent necrosis and perforation of the appendix, emergency appendectomy has been the standard of care since 1889. However, based on epidemiological, immunological and pathology data, several experts have stated(3–6) that appendicitis is not necessarily a progressive disease. Rather, they endorse the idea that two types of appendicitis exist: simple or uncomplicated appendicitis and complicated appendicitis. Over the years, there has been a shift towards non-operative treatment strategies for diseases which were historically treated surgically, for instance, stomach ulcers and uncomplicated diverticulitis. More recently, non-operative treatment (NOT) of acute uncomplicated appendicitis (AUA) has become the subject of investigation. This strategy consists of initial treatment with intravenous antibiotics and reserves appendectomy for non-responders and those with recurrent appendicitis.

Several randomized controlled trials (RCTs) looked at the non-operative treatment of AUA in the adult population. Results, however, vary. Most trials conclude that NOT is safe, but the reported reduction of complications varies from no significant differences(7,8) to up to 86% reduction(9). Recurrent symptoms resulting in delayed appendectomy occur in roughly 1 in 4 patients(7,8,10). These numbers are interpreted in different ways, as is illustrated by the conclusions of three recent systematic reviews, which range from indicating NOT as the preferred treatment(10) to rejecting it as a routine treatment due to insufficient knowledge about its impact on quality of life (QoL)(8).

Approximately one third of all cases of appendicitis occur under the age of 20 years. Regarding the distribution of uncomplicated and complicated appendicitis in the pediatric population, the percentage of uncomplicated appendicitis is reported to range between 68-90% in children aged 5 to 18 years(2,11). The percentage of complicated appendicitis increases with age(12), therefore reducing the amount of patients suitable for initial non-operative treatment strategy. Potential benefits of initial non-operative treatment strategy might therefore be higher for the pediatric population than for the adult population. Data in the pediatric population on the outcome of NOT for uncomplicated appendicitis is scarce and consists mainly of uncontrolled studies with small patient numbers. Recently a systematic review was published, including 10 studies (1 pilot RCT, 6 prospective cohorts and 3 retrospective cohorts) with a total of 413 children treated with NOT(13). Overall complications where reported in 5 of the 6 comparative studies. One out of 175 (0.6%) patients in the NOT group suffered complications vs. 9/239 (3.8%) patients in the primary appendectomy group. Follow-up ranged from 8 weeks to 4 years, with 82% of the NOT patients not having undergone appendectomy at follow-up completion. Recurrent appendicitis occurred in 68/396 (17%) patients; this included 19 children who were treated with a second course of antibiotics.

The evidence regarding the outcome of NOT in the pediatric population is far from sufficient. As of today, apart from the trial described in this article, four large clinical studies (three RCTs(14–16) and one prospective patient preference study(17)) are recruiting children for a comparison of primary appendectomy with NOT. In the Antibiotics versus Primary Appendectomy in Children (APAC) trial we aim to evaluate the effectiveness of the initial NOT strategy (reserving appendectomy for those not responding or with recurrent disease) compared to immediate appendectomy in terms of complications, health-related QoL and costs in children aged 7 to 17 years with AUA.

## Methods and analysis

***Study design***

The APAC trial is a multicenter non-inferiority randomized controlled trial. Blinding was not deemed feasible. The protocol was drafted in accordance with the SPIRIT statements (Standard Protocol Items: Recommendations for Interventional Trials)(18). This trial was registered at clinicaltrials.gov (NCT02848820) and the Dutch Trial Registry (NTR5977) prior to the start of inclusion.

***Patient selection***

Eligible for inclusion are children 7 to 17 years old of both sexes, in whom a imaging-confirmed acute uncomplicated appendicitis is diagnosed in the emergency department of one of the participating hospitals.

*Inclusion criteria*

Definition of AUA is based upon the following criteria.

- Clinical & biochemical criteria:
  - Localized tenderness in the right iliac fossa region
  - Normal/hyperactive bowel sounds
  - No guarding or palpable mass
  - Biochemical signs of infection:
    - Elevated white blood cell count (WBC)
    - Elevated C-reactive protein (CRP)

- Ultrasound criteria to confirm the diagnosis of AUA:
  - A non-compressible, painful appendix with an outer diameter > 6 mm
  - Secondary signs of inflammation, i.e. infiltration of the surrounding fat
  - Hyperemia within the appendiceal wall

In case the ultrasound is inconclusive, additional imaging (MRI or CAT-scan) may be obtained.

*Exclusion criteria*

- Generalized peritonitis or sepsis (as defined by the international pediatric sepsis consensus conference(19))
- Findings on imaging indicative of complex appendicitis:
  - significant and/or unclear free fluid
  - signs of perforation
  - signs of intra-abdominal abscess or phlegmone

- Children with a suspicion of an appendiceal faecalith on imaging studies are excluded, because of its association with a higher risk of NOT failure(20–23).
  Ultrasound characteristics for an appendicalith are defined as a echogenic, well-defined focus within the appendix with posterior acoustic shadowing.
- Serious co-morbidity such as cardiac or pulmonary disease with significant hemodynamic consequences, immunodeficiency, malignancy or sickle cell disease
- A history of non-operatively treated appendicitis
- Suspicion of an underlying malignancy or inflammatory bowel disease
- Documented type 1 allergy to the antibiotics used
- A complex appendicitis risk score indicative of complex appendicitis

*Complex appendicitis risk score*

A pediatric scoring system is used(24) predicting the risk of having complex appendicitis based upon five pre-operative variables; abdominal guarding, signs of complex appendicitis on ultrasound, CRP level, temperature and days of abdominal pain. In an independent validation in a second pediatric cohort a score below 4 had a negative predictive value of 98% (95% confidence interval(CI) 88-100%). Children presenting with a score of 4 or higher will be excluded from this study because of the risk of having complicated appendicitis.

***Randomization***

After written informed consent from parents and child (assent from children under the age of 12) patients are randomized using the web-based randomization program Castor Electronic Data Capture version 4.10(25), stratified by center. A variable block algorithm is used to ensure concealment of allocation.

***Sample size calculation***

A non-inferiority design is used based upon the notion that NOT potentially has secondary advantages, for instance cost reduction and less pain(26). We hypothesize that this might also be the case for QoL. It would thus be sufficient to demonstrate that the outcome in terms of complications is not worse in the NOT group compared to the immediate appendectomy group.
In our pilot study(27) we followed the children eligible for non-operative treatment who refused participation in that study and received immediate appendectomy instead of antibiotic treatment. The frequency of post-operative complications in this group at 1-year follow-up was approximately 10% (unpublished data), meaning that 90% was successfully treated without complications in the operative group. If the difference in complication rate between NOT and operative treatment is less than 5% in favour of appendectomy, non-inferiority is assumed. We will not be testing for the superiority of NOT. Using a 1-sided alpha of 2.5% in accordance with the non-inferiority design, 150 patients per group are needed to achieve 90% power for the exclusion of a difference in favour of the usual care group of more than 5%. Although in our pilot study(27) the drop-out rate after one year was only 2%, we take into account a drop-out rate of 10%. Therefore, the number of patients to be included is 334.

***Study setting and feasibility***

Eligible patients are recruited in 15 hospitals across the Netherlands. This selection consists of both academic and large teaching hospitals. Inclusion started in January 2017. Based on data supplied by

the participating hospitals approximately 225 children per year will meet the inclusion criteria. In our pilot study 57% of eligible patients participated. Taking these numbers into account we expect to include 128 patients per year. We therefore expect to complete inclusion within 32 months. All of the clinical, biochemical and imaging assessments are part of the standard work-up for children suspected of having appendicitis in the Netherlands, as described in the Dutch national guideline(28).

***Interventions***

*Non-operative management*

Antibiotic treatment consists of 48 hours of intravenous (IV) amoxicillin/clavulanic acid 25/2.5 mg/kg 6-hourly (maximum dose: 6000/600 mg per day) and gentamicin (7 mg/kg once daily). When the patient meets the pre-defined discharge criteria after 48 hours (Table 1) he/she is discharged with oral antibiotics. If not, IV antibiotics are continued with a maximum total duration of 72 hours. Oral treatment consists of amoxicillin/clavulanic acid 50/12.5 mg/kg in three daily doses (maximum dose: 1500/375 mg per day). Total duration of antibiotic treatment is 7 days.

| **Pre-defined discharge criteria (equal for both interventions)** | |
|---|---|
| 1. | Body temperature < 38.0 degrees Celsius |
| 2. | NRS <4 |
| 3. | Adequate oral intake |
| 4. | Able to mobilize |
| 5. | Consent of parents for discharge |
| **Pre-defined discharge only for non-operative management** | |
| 6. | Decreased leukocytosis |
| 7. | Decreased C-reactive protein |
| 8. | No signs of complex appendicitis on 2$^{nd}$ ultrasound |

**Table 1. Pre-defined discharge criteria. All criteria have to be met to allow patient to be discharged**

To optimize early detection of NOT failure, WBC and CRP are measured every 24 hours during the time of administration of IV antibiotics. After 48 hours the abdominal ultrasound is repeated to check for signs of complicated appendicitis (Figure 1).

A physician reassesses the patient twice daily. Vital parameters including Numeric Rating Scale (NRS) pain scores are repeated every 6 hours. IV fluid administration is protocolized and weight adjusted, with no oral intake during the first 12 hours. Pain medication is prescribed according to the national guideline(29).

Pre-defined criteria are in place to define the indication for appendectomy (Figure 1). In detail: a WBC count of more than 20 10E9/L or an increasing WBC count after 48 hours are criteria for clinical deterioration. As well as increasing CRP levels after 48 hours. An increasing pain level is defined as a higher NRS score than on admission despite of adequate pain medication according to protocol.

If the patient meets any of these criteria, the decision can be made to proceed with urgent appendectomy or to perform additional imaging studies. This decision is at the discretion of the surgeon in charge of the patients care and does not lie with study coordinators. However, it is

common practice for the treating surgeon to consult with the study coordinators on the appropriate course of action.

**Figure 1. Flowchart non-operative management**

*Operative management*

IV fluids and pain medication is administered according to the same protocol as the NOT group. Antibiotic prophylaxis, operative approach and post-operative care are all according to local protocol. Post-operative antibiotics are only warranted in the event of an unexpected complex appendicitis. Discharge is allowed when the predefined discharge criteria have been met (Table 1).

## Outcome and statistical analysis

***Primary outcome***

The primary outcome is defined as the complication rate at one year follow-up. An independent adjudication committee will review all complications and adverse events to assess their relation to the allocated treatment. The adjudication committee will categorize all complications using the Clavien-Dindo system(30). The Clavien-Dindo system was developed for reporting surgical complications. However, we expect that all possible complications of NOT can also be categorized within the same system, making a comparison between the two groups more consistent. We will report both the overall complication rate as well as subgroups based on complication severity. Any form of delayed appendectomy is not considered a complication, as we consider appendectomy necessary in patients who do not respond to initial non-operative management. This includes early failure during initial admission but also recurrent appendicitis after initial discharge. Complications as a result of a delayed appendectomy are included in the primary outcome.

Complications are defined as, but not limited to:

- Complications of antibiotic use: Allergic reaction with the need for treatment, gastro-intestinal symptoms with the need for treatment, secondary infections, etc.
- Need for surgical or radiological intervention other than appendectomy but related to appendicitis
- Re-admission for an indication other than recurrent appendicitis but related to the allocated treatment
- Complications associated with appendectomy:
    - Surgical site infection: Incisional and organ-space as defined by the CDC criteria(31). We do not differentiate between superficial and deep-incisional infection
    - Stump leakage/stump appendicitis in need of antibiotic treatment or surgical/radiological intervention
    - Secondary bowel obstruction confirmed by imaging or per-operative diagnosis with the need for (non-surgical) treatment. For instance as a result of adhesions
    - Anesthesia related complications, such as pneumonia (in need of antibiotic treatment)
    - Incisional hernia. Defined as any abdominal wall gap with or without a bulge in the area of a postoperative scar perceptible or palpable by clinical examination or imaging

***Secondary outcomes***

The rate of delayed appendectomy is reported as a secondary outcome. To evaluate the secondary endpoints follow-up will take place at 7 days, 4 weeks, 6 months and 1 year after randomization. Other secondary outcomes are listed below.

- Appendectomy related endpoints
  - Percentage of patients not having to undergo appendectomy
  - Percentage of patients with a missed diagnosis of complex appendicitis
  - Percentage of patients having to undergo appendectomy during initial antibiotic course
  - Patients with recurrent appendicitis within 1 year (histopathologically confirmed)
  - Percentage of patients undergoing interval appendectomy (histopathologically no sign of recurrent appendicitis)

- Patient related endpoints
  - Level of pain: assessed with by the NRS and total usage of pain medication on day 7
  - Health-related Quality of Life: assessed with the Child Health Questionnaire-Child Form 87 (CHQ-CF87)(32), the European Quality of Life-5Dimensions-Youth questionnaire (EQ-5D-Y) (child perspective) and European Quality of life-5Dimensions-Proxy questionnaire (EQ-5D-Proxy) (parent perspective)(33)
  - Patient satisfaction assessed with the NET promotor score and the validated Patient Satisfaction Questionnaire (PSQ-18)(34)
  - 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 to the outpatient clinic, general practitioner's office or emergency department for abdominal pain
  - Total length of hospital stay during the follow-up period, including admissions due to complications related to the allocated treatment. The length of initial hospital stay is included but will also be reported separately

- Cost related endpoints
  - Non-medical and indirect costs at one year follow-up: using the Medical Consumption Questionnaire (iMCQ)(35) and the Productivity Cost Questionnaire (iPCQ)(36) adapted for use in children and parents
  - Actual health care costs: variables gathered are, but not are limited to, number of follow-up out-patient clinic visits, number of general practitioner visits, number of emergency department visits and actual in-hospital generated costs

***Data analysis plan***

The primary analysis will be done according to the intention-to-treat (ITT) principle. A per-protocol analysis will be performed as well to prevent unjust rejection of the null hypothesis, which is a risk in non-inferiority research(37). We only consider cases as a treatment arm crossover if the randomly assigned treatment is switched because of patient and/or parental preference without their being medical grounds. Therefore patients receiving an appendectomy because of clinical deterioration, abdominal complaints after discharge, or recurrent appendicitis will be not be labeled as a crossover. We will use multiple logistic and linear regression analyses for binary and continuous outcomes,

respectively, to adjust for stratification factors. Differences in proportions, numbers needed to treat and absolute and relative differences in continuous outcomes will be presented with the corresponding 95% CI, except for the percentage of patients with complications within one year (primary outcome), for which a one-sided 97.5% CI limit will be given in accordance with the non-inferiority design. In a secondary analysis the information recorded during the initial hospital stay will be analyzed using multiple logistic regression analysis in order to identify potential predictive variables for NOT failure. Statistical analyses will be performed using IBM SPSS Statistics Version 22.0 or higher (IBM Corp. released 2013. Armonk, NY).

## Ethics and dissemination.

***Data collection and confidentiality***

All data is handled confidentially and access is strictly limited in accordance with the Dutch Personal Data Protection Act. All participants are assigned a unique study code, which is not based on the patient initials or birth date. The master sheet only contains the study code and patient identification information. Data is gathered through clinical observations, outpatient clinic visits, follow-up phone calls and online questionnaires. All data is collected via Castor Electronic Data Capture(25), a web-based electronic case record form, which is built, maintained and has an audit trail all according to Good Clinical Practice guidelines. All data will be stored for a period of at least 15 years.

***Monitoring and safety***

Reliable high quality data is deemed of the upmost importance. The Clinical Research Bureau of the VU University Medical Centre will provide external monitoring, with monitoring visits of each participating center at least once a year.

The accredited Medical Ethics Review Committee of the Academic Medical Center, Amsterdam (MERC AMC) will be informed annually. All (serious) adverse events, suspected unexpected serious adverse reactions (SUSAR) and any other significant problems are reported to the MERC using an online submission system. To further assure the safety of participants an independent Data Safety Monitoring Board (DSMB) is installed, consisting of a surgeon, a pediatrician and a statistician. They receive an overview of the primary outcome six-monthly, as well as serious adverse events (SAEs), SUSARs and the number of patients having to undergo a delayed appendectomy. An interim analysis for efficacy will not be performed. If a serious concern arises for the safety of the patients in the trial, the DSMB can recommend early termination of the study. These agreements have been documented in a DSMB charter.

***Ethics***

The trial will be conducted in compliance with the current version of the Declaration of Helsinki, the ICH Good Clinical Practice guidelines E6(R1) and in accordance with the Dutch Medical Research Involving Human Subjects Act (WMO). The study protocol has been approved by the MREC AMC.

***Withdrawal***

Subjects can withdraw from the study without explanation at any time. They will be asked their reason for withdrawal, and they will be asked for permission to use their data. In case of withdrawal the patient will be treated according to the national protocol, which would be an appendectomy. However, the surgeon in charge of care can decide otherwise in agreement with the patient and his

or her family. Patients can also be withdrawn by the surgeon or the investigator for urgent medical reasons.

***Dissemination plan***

Dispersion of the trial results will be accomplished by publication in an international peer-reviewed scientific journal and by presentations at (international) conferences. When the results of the trial warrant changes in the standard treatment guidelines of simple appendicitis, we reckon that the widespread execution of the trial in centers throughout the Netherlands will aid in its implementation.

*Implementation study*

To ensure optimal implementation a problem analysis will be conducted parallel to this RCT, investigating the promoting and obstructing determinants of implementation from patients', surgeons', organizational and social-political perspective. This qualitative study will include structured interviews with patients, parents, professionals and other stakeholders.

## Discussion

*Strengths and limitations of this study*

This trial only includes patients with imaging-confirmed appendicitis, thus reducing the risk of including patients with other diagnoses, or those with a non-inflamed appendix. Since the implementation of a guideline in the Netherlands promoting pre-operative imaging, the per-operative finding of non-inflamed appendices was reduced to 3.3%(38), which is low compared to for example the UK, where it is 20.6%(39). We postulate that our use of elaborate and, where possible, evidence-based patient selection methods enhances the chance of successful non-operative management. To warrant the safety of patients undergoing NOT, this protocol dictates systematic and frequent evaluation (by clinical assessment, laboratory tests and imaging studies). We expect this will identify patients not responding to the antibiotic treatment at an early stage.

The non-inferiority design does not allow for a superiority comparison for the rate of complications. The design choice was based on the argument that both treatment strategies are 100% effective in treating appendicitis, because when antibiotic treatment is not successful and when recurrent appendicitis occurs, appendectomy is performed. We postulate that the non-operatively treated patients who do not require appendectomy will have a reduction in costs, better quality of life and the avoidance of the complications associated with appendectomy. Essential for the possible acceptance of this new strategy is that it is not inferior when it comes to the risk of complications. To determine the severity of possible complications and their relation with the allocated treatment we consider the support of an independent adjudication committee a great asset.

The inclusion and exclusion criteria of this trial are mostly based on data that allow for distinguishing complex from uncomplicated appendicitis. Criteria that predict the risk of NOT failure would be more adequate. However, more data and more experience are needed to be able to develop such criteria. Data from the APAC trial will also be used to analyze predictors of failure.

*Choice of primary outcome*

Determining the appropriate primary outcome measure in studies comparing non-operative treatment to operative treatment remains challenging. In our opinion, both strategies will be

effective in treating patients with appendicitis, and therefore effectiveness or failure is not an appropriate outcome measure. Therefore we decided to use a composite outcome measure i.e. complications. Such outcome measures (morbidity and mortality) are necessary in order to start the debate whether or not non-operative treatment strategy can be integrated in clinical practice. Furthermore our goal is to compare the initial non-operative treatment strategy (reserving an appendectomy for those not responding or with recurrent appendicitis) to direct operative treatment strategy. In this view, stating that delayed appendectomy for the indication of failed antibiotic treatment or recurrent appendicitis is a complication would not be appropriate as it is integrated in the treatment strategy. Post-operative complications after delayed appendectomy are however considered as complications of the initial non-operative treatment strategy. The amount of delayed appendectomies (for both non-responders and recurrent appendicitis) needs be included in the debate whether or not initial non-operative treatment strategy can be implemented in daily practice. It is therefore reported as a secondary outcome.

*Complicated appendicitis*

Reluctance of some surgeons towards NOT might be explained by the fear of missing complicated appendicitis and delaying appropriate treatment. In 4.5-6.5% of the adult population treated with NOT who underwent delayed appendectomy, complicated appendicitis was found(7,10). The outcome in terms of post-appendectomy complications after delayed appendectomy (6.9%) is comparable to that for primary appendectomy (8.8%)(8).

*Exclusion of patients with appendiceal faecalith*

We excluded patients with a suspicion of an appendiceal faecalith on pre-operative imaging studies because it is associated with a higher failure rate of NOT. In the adult population a NOT failure rate after one month of 50% was reported in the group with a faecalith vs. 14% in the group without a faecalith(20). One study only including children with appendicitis and a faecalith on imaging had to terminate inclusions early because of a NOT failure rate of 60% at a median of 4.7 months follow-up (23). Faecaliths are also associated with a higher long term recurrence risk in children, with 47.4% recurrences vs 23.7% (21).

*Follow-up/long-term effects*

Information regarding long-term results of NOT in simple appendicitis is limited and it is scarce in children. One study in children with an average follow-up of 4.3 years reported that 22 of 78 (29%) children treated with NOT experienced recurrent appendicitis(21), with a median time to recurrence of 6 months. Eight percent of all non-operatively treated children experienced recurrence after more than 1 year. The APAC trial has a follow-up of 1 year. However, all participants who have not been operated at the end of the study will be asked to participate in long-term follow-up. The long-term effects in children of losing the function of the appendix have also not yet been cleared up. The appendix might play a role in immunity and there is evidence that it is involved in preserving a healthy gut microbiome(40).

*Choice of antibiotic regime*

Most of the data on antibiotic susceptibility in appendicitis is derived from studies in adults, patients with complicated appendicitis, and mixed patient groups. There is some evidence available concerning children. A study analyzing cultures from children in Ireland with complicated appendicitis revealed that the combination therapy of amoxicillin-clavulanic acid and

aminoglycosides would be appropriate in 99% of children with bacterial appendicitis-related peritonitis(41). Since antibiotic resistance rates are greatly dependent on geography, we can expect comparable or even better results in the Netherlands, considering it has the lowest rates of antibiotic use in Europe(42). Combined with a low rate of complications and extensive experience with amoxicillin-clavulanic acid and gentamicin, we consider it the most sensible regime. Further research is carried out by our research group analyzing the microbiome in simple and complicated appendicitis. Hopefully this will contribute in determining the best antibiotic regime. If non-operative treatment of appendicitis is shown to be non-inferior in this trial, further research should determine the most sensible regime and treatment duration. The first pilot RCT evaluating outpatient conservative management in a mixed group (children and adults) has already been published(43).

*Antibiotic resistance*

A possible downside of NOT as opposed to surgery could be increased antibiotic resistance(44). Interestingly, a study evaluating bacterial resistance in complicated appendicitis in children showed no significant increase in resistance rates over the past 20 year(45). How this translates to bacterial resistance when simple appendicitis is treated with antibiotics, is unclear. The use of multi-drug treatment regimens has been pointed out as one of the possibilities to reduce the development of resistant bacteria(46). Our choice for amoxicillin-clavulanic acid and gentamicin prevents us from having to use so-called reserve antibiotics, unlike most of the other know studies in children, in which for instance piperacillin-tazobactam is the drug of choice. Also when the symptoms do not resolve under the chosen antibiotic regimen, appendectomy is performed; we do not switch to other antibiotics.

*Value of histologic evaluation*

An occasionally mentioned argument(8) against non-operative treatment of appendicitis is the risk of missing other underlying causes of appendicitis, such as a carcinoid. One study repeated the abdominal ultrasound in children 1-3 months after NOT to ensure the diameter of the appendix returned to normal(21). The value of this strategy is unknown. In an analysis of 241 histopathologic appendectomy samples in children with simple appendicitis, 4 (1.6%) showed unexpected findings(47). Three parasitic infections and one Walthard cell rest were found; none of the findings required further treatment or investigation. The frequency of appendiceal carcinoid tumors in children undergoing appendectomy was 0.2%(48) and in less than 20% of these cases lymphovascular or mesenteric involvement was present. This seems a negligible risk and it is yet unclear if patients who are excluded or unresponsive to NOT are also the patients with the highest risk of having a malignancy as underlying cause.

Unique for the APAC trial is its primary outcome measure; total number of complications after 1 year. Delayed appendectomy or recurrence is not reported as the primary endpoint or as a complication. Because in our opinion there is a place for the appendectomy in non-operative management as a step-up approach for children unresponsive to antibiotic treatment. As a result eight or nine out of every 10 children with uncomplicated appendicitis would no longer have to undergo an appendectomy. Furthermore if we are able to identify specific predictive pre-operative variables, we might identify a group of patients with even better (long-term) outcomes. Finally this trial should answer the question whether the advantages of NOT are also reflected in the reported quality of life and diminished costs.

## Footnotes

**Collaborators:** The surgical, pediatric, radiology, pharmacy and emergency medicine departments of the following Dutch hospitals contribute to the execution of this trial: Academic Medical Center, Amsterdam, The Netherlands; Ziekenhuis Amstelland, Amstelveen, The Netherlands; Catharina ziekenhuis, Eindhoven, The Netherlands; Elkerliek ziekenhuis, Helmond, The Netherlands; Erasmus Medical Center, Rotterdam, The Netherlands; Flevoziekenhuis, Almere, The Netherlands; Gelre Ziekenhuis, Apeldoorn, The Netherlands; Maxima Medical Center, Veldhoven, The Netherlands; Maastricht University Medical Center, Maastricht, The Netherlands; Noordwest Ziekenhuisgroep, Alkmaar, The Netherlands; OLVG, Amsterdam, The Netherlands; Rode Kruis Ziekenhuis, Beverwijk, The Netherlands; St. Antonius ziekenhuis, Nieuwegein, The Netherlands; University medical center Radboud, Nijmegen, The Netherlands; University Medical Center, Utrecht, The Netherlands; VU University Medical Center, Amsterdam, The Netherlands; Zuyderland, Heerlen/Sittard, The Netherlands.

**Acknowledgments**
Due to the multi-center and multidisciplinary nature of the trial not all supporting researchers can be mentioned by name. However we would like to acknowledge all supporting pediatricians, radiologists, pharmacists, emergency medicine physicians and pediatric nurses. And we would like to thank all of the supporting staff and other physicians that make the realization of this trial possible. We would also like to acknowledge the Dutch Foundation Children and Hospital for their advice and support in drafting the protocol.

**Authors' contributions**: All authors have contributed to the design of this trial protocol. RRG, JHvdL and HAH have initiated the project. LWEvH and RB are the chief investigators. The protocol was drafted by RRG which was refined by JHvdL, SMLT, LWEvH, RB and HAH. Statistical advice was provided by JHvdL. MK was responsible for drafting this manuscript. All authors have contributed to the manuscript and read and approved the final manuscript. The APAC collaborative study group consist of all local investigators who are responsible for the execution of the trial and valid data gathering. They have all read and approved the final manuscript.

**Data sharing statement:**
The trial is registered on ClinicalTrials.gov and the Dutch trial registry, both of which are open access. The study findings will be presented in a report which will be submitted for publication in a relevant peer-reviewed journal to ensure dissemination to relevant healthcare professionals. Findings may also be submitted for presentation at local meetings or conferences. The participant-level data set may be made available for meta-analyses pending relevant Medical Ethics Review Committee approval.

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**Competing interests statement:** None to declare

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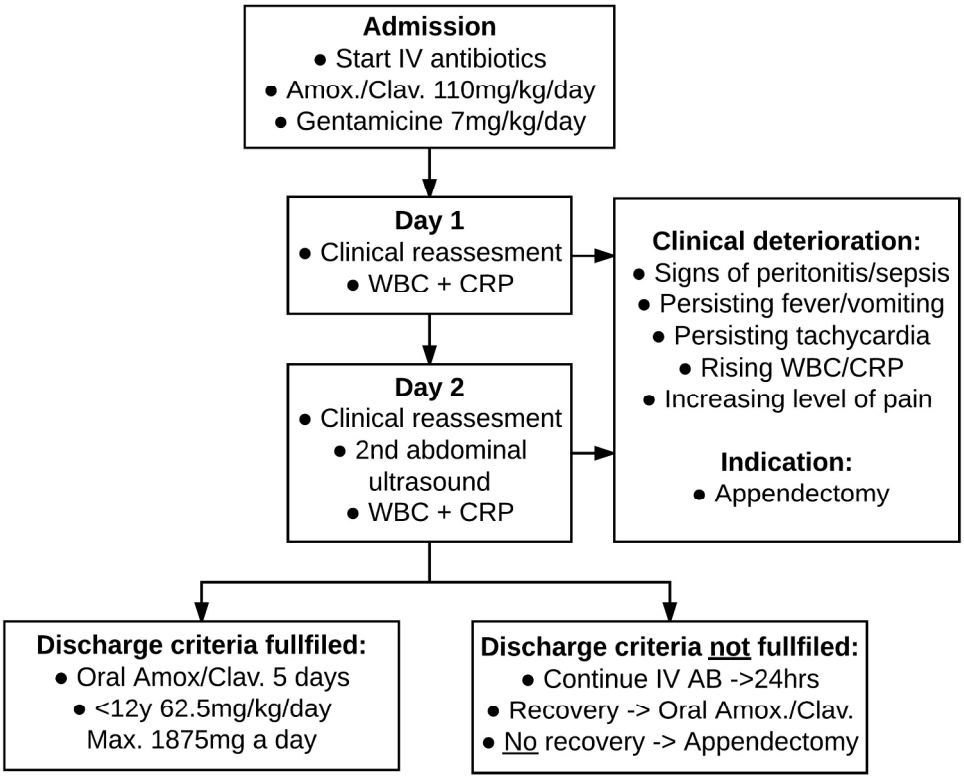


Figure 1. Flowchart non-operative management

217x178mm (300 x 300 DPI)


SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | Item No | Description | Addressed on page number |
|---|---|---|---|
| **Administrative information** | | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry | |
| | 2b | All items from the World Health Organization Trial Registration Data Set | |
| Protocol version | 3 | Date and version identifier | |
| Funding | 4 | Sources and types of financial, material, and other support | |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors | |
| | 5b | Name and contact information for the trial sponsor | |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | |
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | |

**Introduction**

| | | | |
|---|---|---|---|
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention | |
| | 6b | Explanation for choice of comparators | |
| Objectives | 7 | Specific objectives or hypotheses | |
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) | |

**Methods: Participants, interventions, and outcomes**

| | | | |
|---|---|---|---|
| Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained | |
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | |
| | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) | |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) | |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | |
| Outcomes | 12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | |
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | |

| | | | |
|---|---|---|---|
| Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | |

**Methods: Assignment of interventions (for controlled trials)**

| | | | |
|---|---|---|---|
| Allocation: | | | |
| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | |
| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | |
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | |

**Methods: Data collection, management, and analysis**

| | | | |
|---|---|---|---|
| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | |
| | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | |

| | | | |
|---|---|---|---|
| Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | |
| | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | |
| **Methods: Monitoring** | | | |
| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | |
| | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | |
| Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | |
| **Ethics and dissemination** | | | |
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | |
| Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) | |

| | | | |
|---|---|---|---|
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | |
| Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | |
| Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | |
| Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | |
| Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers | |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | |
| **Appendices** | | | |
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates | |
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | |

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. 