

Research protocol:

Non-inferiority multicenter randomized controlled trial comparing short versus standard course postoperative antibiotic treatment for complex acute appendicitis

April 2019

**PROTOCOL TITLE**

Non-inferiority multicenter randomized controlled trial comparing short versus standard course postoperative antibiotic treatment for complex acute appendicitis

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**LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS**

<b>AB</b>	<b>Antibiotics</b>
<b>ABR</b>	<b>ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)</b>
<b>AE</b>	<b>Adverse Event</b>
<b>AR</b>	<b>Adverse Reaction</b>
<b>ASA</b>	<b>American Society of Anaesthesiologists</b>
<b>BMI</b>	<b>Body Mass Index</b>
<b>CA</b>	<b>Competent Authority</b>
<b>CCMO</b>	<b>Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek</b>
<b>CDC</b>	<b>Centre for Disease Control</b>
<b>CRP</b>	<b>C-Reactive Protein</b>
<b>CV</b>	<b>Curriculum Vitae</b>
<b>DSMB</b>	<b>Data Safety Monitoring Board</b>
<b>EAES</b>	<b>European Association of Endoscopic Surgery</b>
<b>eGFR</b>	<b>Estimated Glomerular Filtration Rate</b>
<b>ER</b>	<b>Emergency Room</b>
<b>EU</b>	<b>European Union</b>
<b>EudraCT</b>	<b>European drug regulatory affairs Clinical Trials</b>
<b>GCP</b>	<b>Good Clinical Practice</b>
<b>GP</b>	<b>General Practitioner</b>
<b>IB</b>	<b>Investigator's Brochure</b>
<b>IAA</b>	<b>Intra-Abdominal Abscess</b>
<b>IC</b>	<b>Informed Consent</b>
<b>IDSA</b>	<b>Infectious Diseases Society of America</b>
<b>IMP</b>	<b>Investigational Medicinal Product</b>
<b>IMPD</b>	<b>Investigational Medicinal Product Dossier</b>
<b>iMTA-PCQ</b>	<b>Institute for Medical Technological Assessment – Productivity Cost Questionnaire</b>
<b>IV</b>	<b>Intravenous</b>
<b>LA</b>	<b>Laparoscopic Appendectomy</b>
<b>MA</b>	<b>Marketing Authorisation</b>
<b>MC</b>	<b>Medical Centre</b>
<b>METC</b>	<b>Medical research ethics committee (MREC); in Dutch: medisch ethische</b>

	<b>toetsing commissie (METC)</b>
<b>NA</b>	<b>Not applicable</b>
<b>NEJM</b>	<b>New England Journal of Medicine</b>
<b>NVvH</b>	<b>Nederlandse Vereniging van Heelkunde</b>
<b>OA</b>	<b>Open Appendectomy</b>
<b>OR</b>	<b>Odds Ratio</b>
<b>PO</b>	<b>Per Os</b>
<b>(S)AE</b>	<b>(Serious) Adverse Event</b>
<b>SIS</b>	<b>Surgical Infection Society</b>
<b>SPC</b>	<b>Summary of Product Characteristics (in Dutch: officiële productinformatie IB1-tekst)</b>
<b>Sponsor</b>	<b>The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.</b>
<b>SSI</b>	<b>Surgical Site Infection</b>
<b>SWAB</b>	<b>Stichting Werkgroep Antibiotica Beleid</b>
<b>SUSAR</b>	<b>Suspected Unexpected Serious Adverse Reaction</b>
<b>Wbp</b>	<b>Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgegevens)</b>
<b>WBC</b>	<b>White Bloodcell Count</b>
<b>WMO</b>	<b>Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen)</b>
<b>WSES</b>	<b>World Society of Emergency Surgery</b>
<b>VAS</b>	<b>Visual Analogue Score</b>

## SUMMARY

**Rationale:** Acute appendicitis is an inflammation of the appendix. In the Netherlands, approximately 16.000 patients undergo appendectomy annually. After appendectomy for uncomplicated appendicitis most patients can be discharged within 24-48 hours. However, in 25 – 30% of the patients, a complex appendicitis is diagnosed for which guidelines dictate postoperative intravenous antibiotics to reduce the rate of infectious complications. There is currently no consensus on the duration of postoperative antibiotics and randomized clinical studies are lacking. Cohort studies suggest there is no difference in infectious complications when comparing three to five days of postoperative antibiotics. To minimize hospital stay, costs and the risk of bacterial resistance, it is important to define a safe and effective antibiotic regimen. There is an urgent need for a high-quality study assessing the appropriate duration of postoperative antimicrobial therapy for complex appendicitis in both children and adults.

**Objective:** The goal of this study is to evaluate efficacy and safety of stopping postoperative antibiotic treatment after 48 hours of intravenous therapy *versus* continuing for three more days (to complete a total of five days which is common practice), following appendectomy in patients suffering from complex appendicitis. The primary endpoint is a composite endpoint postoperative infectious complications related to appendectomy, including intra-abdominal abscess and surgical site infection, and mortality within 90 days after appendectomy. Secondary objectives are cost-effectiveness, intra-abdominal abscess, superficial and/or deep surgical site infections, mortality, duration of postoperative antibiotic treatment, re-start of antibiotics, hospital stay in hours from the operation, time to reach discharge criteria in hours from the operation, all postoperative complications, visits to the GP/ER/outpatient clinic,, readmission rate and adverse events on antibiotics (all within 90 days after appendectomy).

**Study design:** Non-inferiority, multicenter, randomized clinical trial comparing two postoperative treatment strategies of antibiotics for complex acute appendicitis.

**Study population:** Patients are eligible for inclusion if they are  $\geq 8$  years of age and have undergone appendectomy (open or laparoscopic) for complex acute appendicitis in one of the participating hospitals. The diagnosis complex appendicitis is made intraoperatively by the surgeon and includes a gangrenous and/or perforated appendicitis and appendicitis with an intra-abdominal or pelvic abscess.

**Intervention:** Patients will be randomized to either A) stopping antibiotic treatment after 48 hours of intravenous antibiotics (intervention group), or B) continuing antibiotic treatment for three more days (control group). Antibiotics given intravenously are cefuroxime and metronidazole, or alternatively ceftriaxone and metronidazole. In children the doses will be adjusted according to their weight.

**Study variables:** Age at time of diagnosis, location of operation, medical history (including diabetes mellitus, corticosteroid use), ASA score, gender, BMI, body temperature and laboratory results at time of presentation (CRP, WBC, renal function (e.g. eGFR or MDRD), diagnostic radiological imaging, duration and severity of abdominal pain (VAS scale), antibiotic use prior to clinical diagnosis of acute appendicitis (type and dosage), prophylactic antibiotic use (type and dosage), laparoscopic or open appendectomy, duration of operation (skin-to-skin time), type of appendicitis (suppurative/phlegmonous, gangrenous or perforated, with or without abscess), degree of peritonitis, level of expertise of surgeon, peritoneal irrigation and/or suction, wound management, use of (endo)loops or (endo)stapler, intraperitoneal drain placement, cultures of intra-abdominal fluid collections, histological type (postoperative) of appendicitis, time to reach discharge criteria, postoperative imaging for suspected complications, intra-abdominal abscess (IAA), deep and/or superficial surgical site infection (SSI), treatment of IAAs and SSIs, any other postoperative complication including severity and treatment, duration and doses of antibiotics received, restart of antibiotics and type, adverse events on antibiotics, type and resistance profile of cultured micro-organisms postoperatively, length of hospital stay, post-operative GP/ER/outpatient visit, readmission, re-interventions for complications (all within 90 days after appendectomy).

**Nature and extent of the burden and risks associated with participation:** Treatment of complex acute appendicitis with the proposed antibiotics is common practice in the Netherlands. Both regimens have been widely used for a long time already and toxicity and possible side effects are well documented. Therefore no extra risks are associated with the medicinal products. The risk of reducing antibiotic treatment in the intervention group in terms of a possibly higher rate of infectious complications is considered low. To closely monitor clinically important adverse events, an independent safety committee (DSMB) is established. Personal benefit for patients in the intervention group in terms of patient comfort may be shorter hospital stay and less antibiotic use. No extra burden is associated with trial-participation in the context of blood samples taken, number of site visits and other physical examination or tests. The only difference compared to standard practice is one extra follow-up by phone and two short questionnaires.

## 1. INTRODUCTION AND RATIONALE

Appendicitis is one of the most common acute gastrointestinal inflammatory disorders in children and adults, often requiring surgery and hospitalization (1). Although the role of surgery as primary treatment has recently been questioned, appendectomy remains the treatment of choice (2, 3). In the Netherlands approximately 16.000 patients undergo an appendectomy for suspected appendicitis annually (4). Two surgical approaches are used to remove the appendix, open appendectomy (OA) and laparoscopic appendectomy (LA). Laparoscopic approach reduces superficial surgical site infections and is associated with shorter hospital stay (5-7). In a study among adult patients, the incidence of intra-abdominal abscesses was increased nearly twofold after laparoscopic as compared to open appendectomy (8), although this was not confirmed in other reviews (9, 10). The choice between OA and LA depends on the surgeon's preference and expertise. In 2001, 8.8% of all appendectomies in the Netherlands were performed laparoscopically, increasing to 21.8% in 2005, 44.2% in 2009 and 74.4% in 2014 (4, 11).

### *Simple versus complex appendicitis*

The clinical presentation of patients with acute appendicitis varies from asymptomatic patients to presence of septicaemia. Acute appendicitis is classified into two distinct types: simple and complex appendicitis. Previously, it was thought that a simple appendicitis could progress to a complex infection, but more recent data show separate types of inflammation (12, 13). Some 25% - 30% of all appendicitis is complex (14-18). Younger age is associated with a higher percentage of perforated appendicitis (15, 19). A recent review paper in the Lancet by Bhangu *et al.* defines simple and complex appendicitis as follows (12):

#### Simple appendicitis:

- Suppurative/phlegmonous
  - o Transmural inflammation, ulceration or thrombosis, with or without extramural pus

#### Complex appendicitis:

- Gangrenous
  - o Transmural inflammation with necrosis
- Perforated
  - o Perforation; macroscopic or microscopic
- Abscess (pelvic/abdominal)
  - o Transmural inflammation with pus, with or without perforation

Complex appendicitis is a risk factor for the development of postoperative infectious complications. Morbidity associated with infectious complications in complex appendicitis is well described, particularly for surgical site infections (19, 20). Postoperative intra-abdominal abscess is the most common complication with an incidence of 5 - 20% (5, 14, 16, 20-25). In children younger than five years old, up to 37.5% develops an intra-abdominal abscess (19). A postoperative intra-abdominal abscess doubles the costs and accounts for one week of extra hospital stay in paediatric patients (26).

An accurate preoperative determination of the severity of appendicitis is difficult. Pathology findings correlate poorly with the intraoperative diagnosis (judgement of the surgeon) of the severity of appendicitis (27, 28). A simple appendicitis was classified as more severe in 70% of patients, whilst a histologically proven complex appendicitis was not diagnosed as such intraoperatively in 10% of patients (27). In this study, operative findings were more predictive of a complicated postoperative course than histology. Hence, postoperative management should be guided by intraoperative findings (27).

## **Antibiotics for appendicitis**

### *Perioperative prophylaxis*

Management of intra-abdominal infections requires in succession 1) resuscitation of patients with systemic inflammatory response syndrome or sepsis, 2) initiate antimicrobial therapy, 3) appropriate source control intervention including surgery or other interventional techniques, 4) maintain or adjust antimicrobial agents to eradicate residual pathogens in complicated intra-abdominal infections (29-31). The role of antibiotic prophylaxis for appendicitis and other intra-abdominal infections has been described extensively in literature.

For intra-abdominal infections like acute appendicitis prophylactic administration of an antimicrobial is recommended and should be discontinued within 24 hours (29, 32). In patients undergoing appendectomy, antibiotic prophylaxis reduces postoperative infections (surgical site infections and intra-abdominal abscess) (32). Hence, antibiotic prophylaxis is recommended in the Dutch guidelines of the Dutch Association of Surgeons (NVvH) and the Dutch Working Party on Antibiotic Policy (SWAB) (33, 34).

In simple appendicitis, the NVvH guideline recommends to give one single dose of antibiotics preoperatively (34). This is in accordance with the guideline by the SWAB: one single dose of cefazoline and metronidazole is recommended (33). A guideline by the Surgical Infection Society (SIS) together with the Infectious Diseases Society of America (IDSA) advises prophylactic administration to be discontinued within 24 hours (29) (See overview of guidelines in Appendix I).

### *Postoperative antibiotic treatment*

In patients suffering complex appendicitis, in addition to perioperative antibiotic prophylaxis postoperative intravenous antibiotics are standard of care. Several studies implicate that postoperative infections, including intra-abdominal abscess, are reduced by perioperative administration of antimicrobial regimes (29, 32). The duration of postoperative antibiotic therapy varies considerably between hospitals.

Guidelines by the SWAB on secondary peritonitis advise 5 - 14 days of intravenous antibiotics, with an option to give an aminoglycoside daily until the cultures are known (33).

The Dutch (NVvH) guideline states that both children and adults should receive antibiotic treatment not shorter than 3 days and not longer than 5-7 days (34). Furthermore, oral antibiotics can be considered after 48 hours of intravenous administration when oral intake is resumed after the operation. These recommendations are mostly based on two papers, a review on appendicitis in children by Snelling *et al.* (2004) and SIS/IDSA guidelines by Mazuski *et al.* (2002) (35, 36). Snelling *et al.* published a review based on both experimental, observational, retrospective, prospective, randomized and nonrandomized controlled trials performed between 1981 and 2001(36). Two small randomized controlled trials were included, in which children received either sulbactam and ampicillin or cefotaxime and metronidazole. In both groups antibiotics were stopped after 3 days resulting in acceptable complication rates (37, 38). However, the aim of these studies was to compare two different antibiotic agents instead of assessing the duration of treatment. The postoperative antibiotic duration was a fixed number of days based upon local preference (hospital protocol). The SIS/IDSA guideline has already been updated in 2010, incorporating new information from this review, even though the methodological quality of the review itself and its included studies is poor (29). The SIS/IDSA recommends that antimicrobial treatment should be limited to 4 – 7 days in this group of patients (29).

And most recently published, the World Society of Emergency Surgery (WSES) guidelines for diagnosis and treatment of acute appendicitis state that a period of 3-5 days of antibiotics should be sufficient (39), although discontinuation should be based on clinical and laboratory results (See overview of guidelines in Appendix I).

As shown in a nationwide cohort study that took place in 2014, by Van Rossem *et al.* (2016), the Dutch guideline on appendicitis and postoperative antibiotic treatment for complex appendicitis is not adhered by many. About 30% of patients received antibiotics for a different duration than initially prescribed and almost 25% of patients were treated with antibiotics for more than five days. The actual total duration of antibiotic treatment varied

between 2 and 10 days (40). The vast majority of patients (approximately 80%) received antibiotics for five or more days.

A randomized controlled trial (STOP-IT-trial) recently published in the *New England Journal of Medicine* by Sawyer *et al.* (2015) showed that in patients with adequate source control of complicated intra-abdominal infections, outcomes after a short course of antibiotic therapy (median 4 days, n=257) were similar to those after a long course (median 8 days, n=260). Surgical site infection, recurrent intra-abdominal infection or death did not differ between the two groups, whilst median duration of antibiotic treatment was significantly shorter in the experimental group (31). Boermeester criticized this study in a commentary published in the *Nederlands Tijdschrift voor Geneeskunde*. The study was stopped prematurely following concerns of futility leading to an underpowered study to demonstrate equivalence (meaning there is a chance that the null hypothesis was rejected based on backward inclusion). Other critical notes were that patients in the study were highly selected, received different antibiotic regimes (based on local hospital protocols) and a quarter of them received antibiotics for a longer duration than defined by the protocol. Some 14% of the patients in the trial had appendicitis (severity was not mentioned, both simple and complex were included). Boermeester concluded that the safety and efficacy of short course antibiotics has not been proven yet (41).

Zakrisson also wrote a commentary on the STOP-IT trial, mentioning the premature discontinuation, but stated that the intention-to-treat and per protocol analyses were both completed. She concluded that given the significant rate of infectious complications in both study groups of more than 20%, other confounders beside duration of antibiotics should be examined in future clinical trials, implying antibiotics may play a smaller role in the prevention of infectious complications than expected (42). Wenzel *et al.* calculated that savings based on the STOP-IT trial (2015) could be more than 97 million per year in the United States (43).

#### No clear consensus in literature

Based on current literature it seems safe to stop intravenous antibiotic treatment earlier than 5 days if the patient meets certain discharge criteria (i.e. patient is afebrile, has a normal leukocyte count, resumed oral intake) (14, 18, 31, 44-49). However, the quality of these studies is often lacking. Based on cohort studies, amongst which one recent large Dutch nationwide prospective study, it seems that 3 days of postoperative antibiotic treatment is feasible and safe (11, 16, 25, 50). No definite recommendations can be made about the safety and efficacy of less than three days of antibiotic treatment, as only a few smaller retrospective studies have been performed in this field (51-54).

In 2015 the European Association of Endoscopic Surgery (EAES) initiated a consensus meeting on the management of acute appendicitis aiming to develop practical European guidelines based on the available evidence combined with the expertise of a selected panel of surgeons (55). It was stated that no recommendation could be made regarding duration nor route of administration of postoperative antibiotic treatment for complicated appendicitis, due to the lack of evidence.

### **Additional reasons for shortening duration of antibiotic treatment**

Apart from the need for consensus on the most adequate duration of therapy, there are several other matters urging for minimizing the duration of antibiotic treatment in patients with a complicated appendicitis.

*Oral route of administration* - Reducing intravenous antibiotics and switching to oral drugs is possible without an increase of complications and was proven to be cost-effective (44, 50, 56, 57). However, other studies found no support for use of oral antibiotics after the initial postoperative intravenous treatment (45, 47). In addition, it is questioned if adequate tissue concentrations can be met by oral antibiotics for the bacteria commonly isolated in complex appendicitis (58).

*Adequate source control* - Recent studies on antibiotic duration in complicated intra-abdominal infection provides support for the concept that the beneficial effects of systemic antimicrobial therapy after adequate source control are limited (31, 59). Experimental studies show that the host immune activity reflects a prolonged systemic inflammatory response syndrome, which is called sterile injury, in contrast to an indication of the presence of viable microorganisms (also known as infection). This suggests that when a systemic inflammatory response syndrome persists after appropriate antimicrobial therapy, it may be due to continuing host damage-associated molecular patterns release (cytokine mediated) rather than persistent infection (60).

*Development of infectious complications is multifactorial* - Antimicrobial therapy is not the only factor of influence, other risk factors for postoperative complications described in literature are: surgical approach (laparoscopic or open), presence of faecolith, diarrhea or bowel obstruction at presentation, preoperative sepsis, high leukocyte count at presentation, weight and/or body mass index, diffuse peritonitis with dominant abscess intraoperatively, duration of operation, conversion to open appendectomy, wound classification (contaminated or dirty), diabetes mellitus and gender (20, 25, 61, 62).

*Antibiotic resistance is an increasingly urgent global health issue* - Resistance is a natural biological outcome of antibiotic use (63). In a report of the World Health Organization the importance of restricting antibiotic treatment was pointed out. Overtreatment was one of the most important reasons for antibiotic resistance (64). Bacteriology of appendicitis includes both aerobic and anaerobic enteric flora and 40 to 60% of all patients has mixed aerobic cultures (65, 66). The most common bacteria associated with acute appendicitis are *E.coli* and bacteria belonging to the *Bacteroides Fragilis* group. Others are *Kleibciella*, *Proteus* and *Pseudomonas Aeruginosa* (66-74). In the Netherlands, cefuroxime is one of the most often prescribed antibiotic in hospitals and most widely used after appendectomy in combination with metronidazole. In 2013, the resistance for cefuroxime among clinical isolates of *E. coli* was 12%, a significant increase from 2009 (75). Metronidazole resistance among anaerobes is rare (75). Chan *et al.* (2010) showed that 25% of paediatric patients with a complex appendicitis in the Hong Kong area were insensitive to a regime consisting of cefuroxime, ampicillin and metronidazole (72). Hence, there is a need for worldwide restriction of unnecessary use of antibiotics.

## CONCLUSION

To sum up:

- medical evidence regarding duration of postoperative antimicrobial therapy for complex appendicitis is lacking and there is no national, let alone international consensus;
- factors such as adequate source control may play a bigger role in prevention of infectious complications than antibiotic treatment;
- battling antibiotic overtreatment is necessary with rising antibiotic resistance worldwide.

All of the above together reflects an urgent need for a high-quality study assessing the appropriate duration in both children and adults.

## 2. OBJECTIVES

The main goal of this study is to establish whether stopping antibiotic treatment after 48 hours following appendectomy with adequate source control for complex acute appendicitis, is safe and effective compared to current standard treatment: five days of intravenous antibiotic treatment.

### Primary objective

Primary objective is a composite endpoint of postoperative infectious complications related to complex appendicitis, including intra-abdominal abscess and both deep and superficial surgical site infection, and mortality within 90 days. A detailed definition of intra-abdominal abscess (IAA) and surgical site infection (SSI) according to the Center for Disease Control (CDC) criteria (76) is given in chapter 8.

Our hypothesis is that stopping antibiotic treatment after 48 hours will not result in a clinically-relevant higher rate of infectious complications compared to current standard antibiotic treatment of five days.

### Secondary objectives

Secondary objectives are:

- *to compare between both trial arms:*
  - o intra-abdominal abscess rate
  - o superficial and/or deep surgical site infections rate
  - o overall postoperative complication rate and severity
  - o duration of postoperative antibiotic treatment
  - o re-start of antibiotics
  - o adverse events on antibiotics
  - o hospital stay in hours from the operation
  - o time to reach discharge criteria in hours from the operation
  - o postoperative imaging for suspected complication
  - o emergency room visits and readmission rate
  - o cost-effectiveness

(all within 90 days after appendectomy)
  
- *to evaluate the external validity and generalizability of the RCT by comparing between study participants and non-participants:*

- baseline characteristics (i.a. age, sex, ASA score, open or laparoscopic appendectomy, degree of peritonitis)
  - duration of postoperative antibiotics
  - hospital stay in hours from the operation
  - intra-abdominal abscess rate
  - superficial and/or deep surgical site infections rate
  - reintervention rate
- to evaluate the use of an informative animated video in the informed consent process by comparing between patients (both participants and non-participants) who did and did not view the video:
- rate of inclusion
  - patient satisfaction with the informed consent process

Secondary endpoints are further specified in Chapter 8.

### 3. STUDY DESIGN

The proposed study is a non-inferiority, multicenter, randomized phase IV clinical trial comparing two antimicrobial treatment strategies for complicated acute appendicitis: short versus standard course of intravenous antibiotics.

Prior to appendectomy, eligible patients diagnosed with (suspected) acute appendicitis will be identified and approached for study-participation. If a complex appendicitis is confirmed intraoperatively and adequate source control is achieved, patients will be randomly allocated to either A) stopping antibiotic treatment after 48 hours of intravenous therapy (the intervention group), or B) continuing antibiotic treatment for three more days to complete a total of five days of intravenous therapy (the control group). See Appendix II: Trial flowchart.

This study is multicenter with 1 academic and several teaching hospitals that have already indicated they are willing to participate pending ethical approval. The proposed starting date is 01-02-2017.

Blinding for treatment allocation in this study would not only be difficult to achieve, but is also undesirable because good clinical decision-making during the postoperative course requires knowledge of the specific interventions that have been given.

#### *Non-participants analysis*

In addition, a non-participants analysis will be performed on all patients eligible for but *not* included in the APPIC trial. The aim of this observational side-study is to be able to evaluate the external validity and generalizability of the APPIC trial.

## 4. STUDY POPULATION

### 4.1 Population (base)

Patients are eligible for inclusion in the RCT if they are diagnosed with (suspected) acute appendicitis, awaiting appendectomy (open or laparoscopic) in one of the participating hospitals. Thereby both simple and complex appendicitis patients will be included into the study (registration) prior to appendectomy. If a complex appendicitis is diagnosed intraoperatively and adequate source control is achieved, patients will be randomized to a treatment arm within the first 24 hours after surgery.

The diagnosis complex appendicitis is made intraoperatively by the surgeon and is defined as follows (according to the classification by Bhangu *et al.* (12)):

- Gangrenous appendix (necrosis)
- Perforated appendix
- Appendicitis with intra-abdominal or pelvic abscess

A short intraoperative video or static picture(s) should be recorded for quality assurance. Pus and pus-like intra-abdominal fluids should be cultured, as is standard of care. Adequate source control is defined as follows: the majority of the contaminated intraperitoneal contents (pus, faeces, necrotic material) is removed to the extent that no further intervention is felt necessary (by the surgeon) besides postoperative antibiotic treatment.

Participating surgeons will be trained on how to adequately assess the severity of appendicitis and when to enroll patients in the study by means of a teaching video, showing recorded examples of all types of appendicitis. Surgical techniques that are effective to achieve adequate source control will be a part of this teaching video as well. An expert committee consisting of surgical residents and surgeons will teach and instruct colleagues prior to the study. All participating hospitals are visited every 6 months for re-education.

A total of 1066 patients must be included (See 4.4 Sample size calculation). We intend to fulfill inclusion within 45 months. The duration is estimated based on the prevalence of complex appendicitis in the Netherlands (25 – 30% of all appendectomies). Annually, approximately 16.000 adults and children in the Netherlands undergo an appendectomy under suspicion of acute appendicitis. Roughly 1.250 of these are performed in the Rotterdam area, of which about 300 involve complex appendicitis. We intend to recruit additional hospitals outside the training region of Rotterdam to join the study, in which case the targeted inclusion rate will be sufficient to reach the sample size within time.

## 4.2 Inclusion criteria

- age minimum 8 years old (no upper limit)
- patients with suspected acute appendicitis, awaiting appendectomy
- written informed consent
- intraoperative diagnosis of a complex appendicitis (as defined at 4.1)

## 4.3 Exclusion criteria

- appendectomy à froid
- not able to give informed consent (language barrier, legally incapable)
- clinical suspicion of severe sepsis, defined as sepsis-induced tissue hypoperfusion or organ dysfunction (any of the following\* thought to be due to the infection (77)):
  - o sepsis-induced hypotension
  - o lactate above upper limits laboratory normal
  - o urine output <0.5 mL/kg/h for more than 2h despite adequate fluid resuscitation
  - o acute lung injury with PaO<sub>2</sub>/FiO<sub>2</sub> <250 in the absence of pneumonia as infection source
  - o acute lung injury with PaO<sub>2</sub>/FiO<sub>2</sub> <200 in the presence of pneumonia as infection source
  - o creatinine >2.0 mg/dL (176.8 µmol/L)
  - o bilirubin >2mg/dL (34.2 µmol/L)
  - o platelet count < 100,000 µL
  - o coagulopathy (international normalized ratio (INR) > 1.5)
- \* *laboratory tests listed above aren't necessarily performed in all patients, some may have been performed if clinically indicated. If performed, they can may support suspicion of severe sepsis.*
- conservative treatment of acute appendicitis
- ASA score IV or not able to undergo surgery
- known allergy to study medication (when in doubt, a microbiologist should be consulted for advice).
- any other contraindication for the use of the study medication (e.g. patients with advanced renal failure)
- immunocompromised patients (i.e. haematological malignancies, HIV/AIDS, bone marrow transplantation, splenectomy, genetic disorders such as severe combined immunodeficiency, chemotherapy, dialysis, solid organ transplant and immunosuppressant use (such as corticosteroids in patients with rheumatoid arthritis))
- pregnancy
- use of other antibiotics for other reason than mentioned in above.
- simple acute appendicitis
- intraoperative appendicular infiltration not amendable for appendectomy
- inadequate source control in the opinion of the surgeon (as defined at 4.1)

### *Non-participants analysis*

Patients who are eligible according to the inclusion and exclusion criteria but do not participate in the APPIC trial, will be included in the observational non-participants analysis. Non-participants that do not receive any postoperative antibiotics will be excluded from this analysis.

## **4.4 Sample size calculation**

This study has a non-inferiority design in which the rate of infectious complications related to appendectomy (primary endpoint) must not be clinically-relevant higher in the intervention group than in the control group. When this condition is fulfilled, the potential advantages of the intervention group strategy become dominant: patient well-being in terms of shortened hospital admission, less costs, less antibiotic resistance and other side effects. In a Dutch study (519 patients with complex appendicitis among 1901 appendectomies), postoperative infectious complications were diagnosed in approximately 18% (78). Invasive diagnostics and treatment in the complex appendicitis group with and without complications consisted of prolonged hospital stay, readmission (10%), re-interventions including radiological (4%) and surgical (4%) approaches, and prolonged administration of intravenous antibiotics (5%). No mortality due to postoperative complications was reported (78). We found similar rates in a retrospective analysis of 637 patients in the Rotterdam area (79). In literature, postoperative infectious complications are reported in 15-20% of patients (19, 80-82). Furthermore, Sawyer *et al.* used a non-inferiority margin of 10% to detect non-inferiority in complication rates after a shorter course of postoperative antibiotic treatment in complicated intra-abdominal infections (31). Based on these findings and the fact that a reduction in antibiotic consumption will lead to reduction in costs and antimicrobial resistance we will accept a 7.5% difference (non-inferiority margin) in the primary endpoint rate between the intervention group and the control group. A non-inferiority trial with this margin is acceptable based on the assumption that complications after an appendectomy for a complex appendicitis have minimum consequences in terms of severe morbidity and/or mortality. Under the presumption that the rate of infectious complications will be 15% in the control group, an increase in the primary endpoint rate of 7.5% corresponds with 22.5% in the intervention group. A power analysis was performed using simulation, based on a one-sided 97.5% confidence interval for the effect (risk difference) of the study group (intervention or control) (83), adjusted for severity of disease and age. Non-inferiority will be established if the upper limit of this confidence interval is lower than 7.5%. To obtain a power of 90%, 960 (480 patients per treatment arm) are needed. To account for the possible effects of dropout and

missing data (10%), we will recruit a total of 1066 patients. This sample size should also yield sufficient power for the analysis of the secondary endpoints.

## 5. TREATMENT OF SUBJECTS

### 5.1 Investigational product/treatment

The intervention is to shorten duration of standard postoperative treatment for complex appendicitis, by stopping after 48 hours of intravenous antibiotic therapy. In the control group standard therapy will be practiced, which means continuing antibiotic treatment for another three days to reach a total of five days of antibiotic treatment. Patients in both trial arms will undergo treatment with medicinal products that are common practice and standard of care for complex appendicitis (in standard dosages as well). Thus, the trial does not concern any investigational products.

Intravenous (IV) antibiotic therapy will consist of cefuroxime and metronidazole. Depending on the time of surgery and local hospital protocol, the first dose of intravenous treatment will be given somewhere within the first 8 hours after appendectomy.

As an alternative to cefuroxime/metronidazole (IV), the combination of ceftriaxone and metronidazole (IV) is allowed, if preferable due to local bacterial resistance patterns.

No other antibiotic regimen is allowed. Unless, however, intraoperative culture results come back with micro-organism(s) resistant to cefuroxime (or to ceftriaxone) before the assigned 48 hours or 5 days of therapy are finished. If this is the case, a switch to another regimen may and should be made to ensure good coverage for the individual patient. Local microbiologists should be consulted to choose the optimum regimen to switch to.

See chapter 7 for more detailed information regarding the above mentioned antibiotics, dosages and administration.

### 5.2 Use of co-intervention (if applicable)

Prophylactic antibiotics will be given perioperatively according to local hospital protocol, as is standard of care. A daily dose of intravenous gentamicin (aminoglycoside antibiotic) is optional and may be given upon indication according to local hospital protocol (e.g. in case of sepsis), as is in line with guidelines(84). No other antibiotics are permitted. Patients can use other medication like pain medication (see escape medication). No restrictions are made based on food, drinks and daily activities.

### **5.3 Escape medication (if applicable)**

Patients are allowed to use medication other than antibiotics according to local hospital protocols, such as the following:

- Any pain medication
- Any antiemetic medication
- Any anti-allergy medication

## **6. INVESTIGATIONAL PRODUCT**

Not applicable (NA).

**6.1 Name and description of investigational product(s) NA**

**6.2 Summary of findings from non-clinical studies NA**

**6.3 Summary of findings from clinical studies NA**

**6.4 Summary of known and potential risks and benefits NA**

**6.5 Description and justification of route of administration and dosage NA**

**6.6 Dosages, dosage modifications and method of administration NA**

**6.7 Preparation and labelling of Investigational Medicinal Product NA**

**6.8 Drug accountability NA**

## 7. NON-INVESTIGATIONAL PRODUCT

### 7.1 Name and description of non-investigational product(s)

- Cefuroxime (Zinacef) 1500 mg. Powder for reconstitution as an intravenous injection or infusion. The cefuroxime is present as cefuroxime-sodium;
- *Alternative to cefuroxime:* Ceftriaxone (Rocephin) 2000 mg. Powder for solution for infusion. The ceftriaxone is present as sodium-ceftriaxone.
- Metronidazole (Flagyl) 500 mg/100 ml suspension for intravenous use (5mg/ml).

Cefuroxime is an antibiotic of the cephalosporin-type (second generation), effective against many gram-negative and gram-positive organisms. Furthermore, it is resistant to inactivation by betalactamases, produced by gram-negative bacteria.

Ceftriaxone is an antibiotic of the cephalosporin-type as well (third generation), also effective against a great variety of gram-negative and gram-positive organisms.

Metronidazole is an antibiotic of the nitroimidazole-class. Metronidazole in itself does not have a direct antimicrobial effect. However it creates a stable and impermeable environment, in which nitrosoradicals are formed under anaerobic conditions. These radicals cause disruption of DNA in anaerobic micro-organisms.

For more details, see Summary of Product Characteristics (SPC) in attachment D2.

### 7.2 Summary of findings from non-clinical studies

See Summary of Product Characteristics (SPC) in attachment D2.

### 7.3 Summary of findings from clinical studies

See Summary of Product Characteristics (SPC) in attachment D2.

### 7.4 Summary of known and potential risks and benefits

In patients with complex appendicitis, both Dutch and American guidelines state that antibiotic regimen should consist of empiric broad-spectrum therapy with activity against

gram-negative rods and anaerobic organisms. In the Netherlands, the Dutch Working Party on Antibiotic Policy (SWAB) suggests to choose between the following three antibiotic regimens (33):

- Ceftriaxone or cefotaxime or cefuroxime in combination with metronidazole (IV)
- Amoxicillin in combination with metronidazole (IV)
- Amoxicillin-clavulanic acid (IV)

It is optional to add an aminoglycoside IV with either regimen.

The combination of cefuroxime and metronidazole - applied intravenously in the dosages mentioned at 5.1 and 7.6 - is most widely used in the Netherlands and is also suggested in the guidelines by the Surgical Infection Society and the Infectious Diseases Society of America (SIS/IDSA) (29). Therefore cefuroxime and metronidazole were chosen as intravenous antibiotic treatment (See Appendix I for an overview of all available guidelines).

Since bacterial resistance patterns differ somewhat between regions in the Netherlands, the combination of ceftriaxone is allowed as an alternative for cefuroxime in this study. This combination is also widely used in the Netherlands and in line with all guidelines.

The SWAB guideline points out that the STOP-IT trial has shown that 4 days may suffice in case of adequate source control, however their recommendation for duration of antimicrobial therapy remains 5-14 days. The SIS/IDSA guideline recommends duration of 4-7 days, adding that antibiotics should be stopped in patients whose symptoms and signs of infection have resolved. This usually implies that the patients are afebrile, have normal white blood cell counts and are tolerating an oral diet (29, 85). And the Dutch (NVvH) guideline recommends duration of 3-5 days (See chapter 1 and Appendix I).

Total treatment duration of 5 days in the control group is chosen because this is in line with current guidelines and best reflects standard treatment in the Netherlands, as shown in a recent nationwide study (about 80% of patients received 5 or more days of antibiotics) (78).

As pointed out in chapter 1, current literature indicates that treatment duration of three days is equally as effective and safe as five days of treatment. Moreover, 48 hours of intravenous administration is sufficient to reach adequate tissue concentrations for the bacteria commonly isolated (such as *E. coli*). Adding one day of oral administration after initial 48 hours of intravenous treatment is not thought to be of benefit. Furthermore there is growing evidence that adequate source control may play a bigger role than antibiotic treatment and patients do not benefit from follow-up with oral antibiotics at all after initial intravenous treatment (31, 45, 47, 58-60). Hence, two days of intravenous administration in the intervention group is chosen.

Potential beneficial outcomes of the shortened antibiotic regime, as described in more detail in chapter 1, could be: less antibiotic use, less antibiotic overtreatment, less antibiotic resistance, shorter duration of hospital stay, decreased hospital costs.

A potential risk might be a higher prevalence of infectious complications that would represent undertreatment. However, morbidity associated with infectious complications after appendectomy is generally mild and IAAs and SSIs can be treated well without long-term consequences.

## **7.5 Description and justification of route of administration and dosage**

Choices of route of administration and dosages in this study are based on Dutch and international guidelines. The intervention only concerns the duration of therapy, other than that standard routes of administration and dosages for the indication complex appendicitis are followed. Intravenous antibiotic therapy will consist of cefuroxime (adults: 1500 mg 3 doses per day) and metronidazole (adults: 500 mg 3 doses per day). Or, alternatively, ceftriaxone (adults: 2000 mg 1 dose per day) and metronidazole (adults: 500 mg 3 doses per day). Children will receive adjusted dosages (See 7.6).

Although guidelines suggest a switch to oral formula can be made after 48 hours, a choice was made not to incorporate so-called switch- or stepdown therapy to oral formula in the control group for several reasons listed below.

First of all, there is no ideal oral agent to switch to. Cefuroxime in oral formula (PO) is not an option, neither is ceftriaxone PO. The NVvH and SWAB guideline do not specify an oral agent to switch to. In the Netherlands amoxicillin-clavulanic acid is given most often as step-down oral antibiotic for abdominal infections. However, as stated before, this antibiotic does not reach sufficient tissue concentrations for bacteria most often isolated (86, 87). Therefore a different antibiotic regimen would be necessary, ciprofloxacin or levofloxacin with metronidazole for instance, regimens that are not common practice in most Dutch hospitals. Incorporating such an oral regimen in the study design would mean asking participating hospitals to change their protocols.

Secondly, we feel that allowing the 'freedom' of switch-therapy might evoke (more) protocol violations, such as prolonging therapy in the intervention group or shortening therapy in the control group. A strict and clear treatment schedule, two versus five days IV will be better adhered to.

Thirdly and most importantly, allowing oral therapy would result in considerable heterogeneity in our control group. Patients would receive varying amounts of intravenous

and oral doses, and compliance to oral therapy would be an uncertain factor. From a methodological perspective this would leave us with a less powerful study and in the end: unable to prove non-inferiority of 2 days IV versus 5 days IV. In order to conduct a methodologically powerful study with meaningful results, we have chosen to compare two days IV versus five days IV therapy.

## 7.6 Dosages, dosage modifications and method of administration

Study drug should consist of cefuroxime IV (adults: 1500 mg 3 doses per day) and metronidazole IV (adults: 500 mg 3 doses per day). The intervention group will receive a total of 6 doses of cefuroxime and metronidazole, whereas the control group will receive 15 doses of cefuroxime and 15 doses of metronidazole.

Or, alternatively, the regimen consists of ceftriaxone (adults: 2000 mg 1 dose per day) and metronidazole (adults: 500 mg 3 doses per day). In which case the intervention group will receive 2 doses of ceftriaxone and 6 doses of metronidazole, whereas the control group will receive 5 doses of ceftriaxone and 15 doses of metronidazole.

In children the following dosages should be administered:

- IV cefuroxime 100 mg/kg/day, max 4.5g/day, in 3 doses/day (88)(89)
- *Alternative to cefuroxime:* IV ceftriaxone 100 mg/kg/day, max 2g/day, in 1 dose/day (90)(91)
- IV metronidazole 30 mg/kg/day, max 1.5g/day, in 3 doses/day (92)(93)

## 7.7 Preparation and labeling of Non-investigational Medicinal Product

In this trial, medicinal products are used that are already registered for the use in intra-abdominal infections and in particular post-appendectomy. Commercially available non-investigational medicinal products are used that have a marketing authorization (MA). Both antibiotics in this trial are standard of care in the Netherlands and have been prescribed for complex appendicitis for decades. As the proposed intervention is to stop antibiotic treatment early (after 48 hours) and in doing so to administer less of the non-investigational products compared to current standard therapy for complex appendicitis, no preparation or labeling of medicinal products is necessary.

## 7.8 Drug accountability

Medicinal products will be used as in usual clinical practice. These antibiotics are present and available in stock at the different departments in all participating medical centres. The (hospital) pharmacist that works in collaboration with the hospital the patient is treated in will provide all medication.

## 8. METHODS

### 8.1 Study parameters/endpoints

#### 8.1.1 Main study parameter/endpoint

Primary endpoint is a composite endpoint of infectious complications related to complex appendicitis, including intra-abdominal abscess and both deep and superficial surgical site infection, and mortality within 90 days after appendectomy.

- *Definition intra-abdominal abscess (IAA)*: an infection that involves the abdominal part of the body deeper than the fascial/muscle layers, that is opened or manipulated during the operative procedure. Patient has at least one of the following (76):
  - o purulent drainage from a drain that is placed into the abscess.
  - o organisms isolated from an aseptically-obtained culture of fluid or tissue in the abscess.
  - o other evidence of an abscess involving the abdominal cavity detected:
    - upon direct examination, or during reoperation;
    - by histopathologic examination;
    - or radiologic examination (fluid collections suspicious for infection due to shape of (enhanced) cavity walls, presence of debris, loculations(94))
  - o diagnosis of an IAA by a surgeon or attending physician.
  
- *Definition superficial and/or deep surgical site infection (SSI)*: an infection that occurs after surgery in the part of the body where the surgery took place. Superficial and deep surgical site infections involve skin, subcutaneous tissue and/or deep soft tissues of the incision. Patient has at least one of the following (76):
  - o purulent drainage from the superficial or deep incision.
  - o organisms isolated from an aseptically-obtained culture from the superficial incision or subcutaneous tissue.
  - o a superficial or deep incision that is deliberately opened or aspirated by the surgeon, or spontaneously dehisces, *and* is culture-positive or not-cultured, *and* the patient has at least one of the following signs or symptoms of infection: fever (>38° C), localized pain or tenderness, swelling, erythema, or heat. A culture-negative finding does not meet this criterion.
  - o diagnosis of a superficial or deep incisional SSI by the surgeon or attending physician.

- *Definition mortality*: death, within 90 days after appendectomy.

### 8.1.2 Secondary study parameters/endpoints (if applicable)

- \*Intra-abdominal abscess (IAA)
  - o as defined at 8.1.1
- \*Superficial and/or deep surgical site infection (SSI)
  - o as defined at 8.1.1
- Mortality
  - o as defined at 8.1.1
- \*Duration and total doses of postoperative antibiotic treatment
  - o The total number of days using antibiotics and the total amount of doses used in both the intervention and control group.
- Re-start of antibiotics
  - o If antibiotics should be restarted after the initially assigned postoperative treatment period, this will be registered. The indication and duration of this additional antibiotic course must be documented.
- \*Hospital stay in hours from the operation
  - o Hospital stay is calculated from day 0 (the procedure day) in hours.
- Time to reach discharge criteria in hours from the operation (95):
  - o body temperature < 38° for 12 hours or more
  - o able to tolerate oral intake
  - o able to mobilize independently
  - o VAS (Visual Analogue Score) pain score < 4, requiring only oral analgesia.Time to reach these criteria is documented in hours from the operation.
- All postoperative complications
  - o including when they occur and how they are treated
  - o graded according to the Clavien-Dindo classification (96)

- classified according to the Comprehensive Complication Index (97)
- Visits to the general practitioner (GP), emergency room (ER) and/or outpatient clinic; and \*readmission rate
  - Any unplanned visit to the GP, ER or outpatient clinic within 90 days after appendectomy will be documented to calculate a potential readmission rate from.
  - Rate of actual readmissions, as well as reasons for and treatment during readmission and duration of readmission stay (in hours) will be registered.
- Adverse events on antibiotics
  - see section 9.2
- Cost-effectiveness (within 90 days after appendectomy)
  - Economic evaluation: the economic evaluation will assess the cost-effectiveness of the reduced versus standard postoperative antibiotic treatment in patients with a complex acute appendicitis over a period of 90 days after surgery.
  - Cost-analysis: the economic analysis will be based on the healthcare perspective as well as the societal perspective.
  - Budget impact analysis: analysis taking into account the changes in medical consumption that might be the result of shorter courses of antibiotics.

### 8.1.3 Other study parameters (if applicable)

Preoperative parameters (at time of presentation)

- \*Age at time of diagnosis
- Unique study number identification number
- Group assignment
- \*Location of operation (Clinical site)
- History patient / comorbidities
  - Cardiac disease
  - Cerebrovascular disease
  - Corticosteroids use
  - Diabetes mellitus (IDDM / NIDDM)
  - Liver disease
  - Malignancy
  - Peripheral vascular disease

- Pulmonary disease
- Renal failure (dialysis)
- Renal insufficiency
- Smoker-present
- Ventilator dependence
- \*ASA score
- \*Sex
- \*Body mass index (BMI)
- \*Body temperature
- Laboratory results
  - \*serum C-reactive protein (CRP)
  - \*serum white bloodcell count (WBC)
  - estimated Glomerular Filtration Rate (eGFR))
- Diagnostic radiological imaging:
  - whether an ultrasound, CT-scan and/or other imaging has taken place.
  - results of all imaging, categorized as one of the following:
    1. appendicitis acuta suspected to be simple
    2. appendicitis acuta suspected to be complex
    3. inconclusive (appendix seen)
    4. inconclusive (appendix not seen)
    5. no signs of appendicitis acuta.
- Duration of abdominal pain (in hours)
- Severity of abdominal pain at presentation (Visual Analogue Scale)
- Antibiotic use prior to appendectomy at home or at the ER (type and dosage),

#### Perioperative parameters

- Prophylactic antibiotic use (type and dosage)
- \*Laparoscopic or open appendectomy
- \*Duration of operation (skin-to-skin time)
- \*Type of appendicitis (suppurative/phlegmonous, gangrenous or perforated, with or without abscess)
- \*Degree of peritonitis (none, loculi of infection/pus or faeces localized, loculi of infection/pus or faeces in Douglas, loculi of infection/pus or faeces spread to four quadrants in the abdominal cavity (diffuse)) (98)
- Level of expertise of surgeon (resident, specialist)
- Peritoneal irrigation
- Peritoneal suction

- Wound management
  - o None (percutaneous drainage)
  - o Primary closure
- Method of stump closure: use of endoloops or stapler or other techniques
- Intraoperative drain placement
- Culture of intra-abdominal fluid (whether a swab has been taken and if so: what micro-organisms are grown)

#### Postoperative parameters

- Histological type of appendicitis
- Discharge criteria
  - o Body temperature < 38°C for 12 hours
  - o Able to tolerate oral intake
  - o Able to mobilize independently
  - o VAS (Visual Analogue Score) pain score < 4, requiring only oral analgesia
- Hospital stay (day of operation = day 0)
- Imaging for suspected complication
- \*Need for re-intervention
- Mortality within 90 days after appendectomy
- Cultures of postoperative IAA and/or SSI (whether a swab was taken and if so: what micro-organisms are grown)
- Related to resistant organism:
  - o MRSA (methicillin- or oxacillin-resistant *Staphylococcus aureus*)
  - o VRE (vancomycin-resistant *Enterococcus faecium* or *faecalis*)
  - o *Clostridium difficile*
- Related to antibiotics:
  - o Resistance
  - o Toxicity
  - o Diarrhoea
  - o Phlebitis
  - o Allergic reaction
- Treatment of IAA or superficial and deep SSI
  - o Radiological drainage
  - o Antibiotic treatment
  - o Surgical procedure
  - o Observation only

*Non-participants analysis*

A selected subset of parameters will be collected from non-participants included in the observational non-participants analysis: all parameters above that are marked with an asterisk (7 preoperative, 4 peroperative and 5 postoperative characteristics).

**8.2 Randomisation, blinding and treatment allocation**

To minimize selection bias, informed consent should preferably be obtained prior to appendectomy, allowing randomization to take place as soon as possible after intraoperative diagnosis of a complex appendicitis. Eligible patients, and/or parents of eligible patients in case of underage, will be approached and informed about the study at the emergency room, prior to appendectomy. If preoperative in- and exclusion criteria (as listed at 4.2 and 4.3) are met including written, voluntary informed consent having been obtained, they will be enrolled into the study (See the trial flowchart in Appendix 2). This means that both simple and complex appendicitis patients may initially be registered. All patients will undergo appendectomy, either open or laparoscopic depending on local protocol and surgeon's preferences, as is standard of care. If complex appendicitis is diagnosed by the surgeon and none of the intraoperative exclusion criteria apply (as listed before at 4.3), the patient will remain in the trial.

Computerized block randomization for allocation of treatment group (stratified for center) will take place within 24 hours after surgery through ALEA, a web-based application managed by the Clinical Trial Centre of the Erasmus MC. A trial website will be constructed with a link to ALEA (<https://prod.tenalea.net/emc/DM>). Patients will be randomized 1:1 to arm A or arm B. Each patient will be given a unique patient study number (a sequence number by order of enrollment in the trial). Patient study number and result of randomization will be provided through ALEA immediately per email to all parties defined in the system that should receive such notifications.

It might occur that an eligible patient has not been approached prior to appendectomy, or has had too little time for proper informed consent, but turns out to fit all in- and exclusion criteria during or shortly after appendectomy. These patients should be asked to participate in the trial after surgery when the patient has recovered from anesthesia but within 24 hours after surgery. Informed consent and randomization will take place as stated above.

### 8.3 Study procedures

Both trial treatment strategies are equal with the only difference being the duration of therapy. All patients will receive the same treatment (intravenous antibiotic therapy) during the first 48 hours. After 48 hours their antibiotic treatment will be A) stopped, or B) continued for three more days. In the postoperative course daily monitoring of body temperature, oral intake, pain medication and VAS pain scores will be registered. Laboratory tests, imaging studies and blood cultures will only be performed when clinically indicated. When the following discharge criteria are met, patients may be discharged from the hospital (95). These criteria are not mandatory though, it is up to the clinician's individual decision to discharge the patient.

- body temperature < 38° for 12 hours or more;
- able to tolerate oral intake;
- able to mobilize independently;
- VAS (Visual Analogue Score) pain score < 4, requiring only oral analgesia.

The time to reach each of these criteria will be documented.

#### *Intervention group*

In the intervention group antibiotic treatment will be stopped 48 hours after surgery (6 doses of cefuroxime and metronidazole, or 2 doses of ceftriaxone and 6 doses of metronidazole). Regardless of whether discharge criteria are reached, the antibiotic treatment will be stopped at this point in time. A raised body temperature or raised pulse rate alone is not an indication for continuation or restart of antibiotics, since this could well be a persisting SIRS-response not reflecting infection (99) . Prolonging or restarting antibiotic treatment can be considered in patients with:

- temperature >39.0°C and/or
- positive blood cultures and/or
- clinical suspicion of sepsis, two or more symptoms are required (77):
  - body temperature <36.0°C or >38.0°C
  - heart rate higher than 100 beats per minute
  - respiratory rate higher than 20 breaths per minute
  - white blood cell count <4x10<sup>9</sup> or >12x10<sup>9</sup> cells/L

Patients should undergo laboratory tests and/or imaging studies according to the Dutch guideline. Antibiotic treatment may only be restarted in case there is a proven source of infection as a clear indication for antibiotic therapy (See decision algorithm in Appendix III). If this is the case, it should be clearly documented.

If infectious complications occur, cultures are taken from IAA's or SSI's to analyze the sensitivity of antibiotics and to compare to the cultures potentially taken perioperatively. This is standard of care and will not result in extra burden for the patient. Swabs and cultures will be analyzed in the laboratory that is in co-operation with the hospital where the appendectomy is performed. Results of the swabs are visible for the data-analyst as well as practitioners, because known resistance could lead to a change in antibiotic treatment.

#### *Control group*

In the control group intravenous antibiotic treatment will be continued to complete five days in total (15 doses of cefuroxime and metronidazole, or alternatively 5 doses of ceftriaxone and 15 of metronidazole). Patients may be discharged from hospital when discharge criteria (as listed above) are reached or when the responsible clinician feels comfortable. With regards to prolonging/restarting antibiotics and complications, the same applies for the control group as stated above for the intervention group.

#### *Follow-up*

At discharge, written and oral instructions to the patient are given according to local hospital protocol. A standard outpatient visit will be planned two to four weeks after appendectomy (according to local hospital protocol).

- Four weeks after appendectomy patients will be asked to complete a Productivity Cost Questionnaire (PCQ). They will receive this questionnaire via email or via regular mail if no email address is available. An additional short questionnaire concerning the informed consent process and use of an informative animated video will be sent along with the PCQ.
- Finally, a follow-up by telephone will be conducted 90 days after appendectomy to minimize loss-to-follow up and check for possibly missing data primarily regarding the primary endpoint. endpoint.

All of the above mentioned procedures and tests are standard of care, and in accordance with current clinical practice for appendicitis in the Netherlands and worldwide. Participants are not submitted to extra invasive procedures. The only extra burden for the patient will be the questionnaire(s) and the extra follow-up by phone.

#### *Non-participants*

Non-participants will undergo standard treatment according to local protocol. A standardized, electronic logbook will be kept of all eligible non-participants, including (preoperative or intraoperative) reasons for non-participation.

At four weeks after appendectomy, a short questionnaire concerning the informed consent process and use of the informative animated video will be sent to non-participants who:

- were treated in 1 of the following 6 centers: Erasmus MC, Franciscus Gasthuis & Vlietland, Reinier de Graaf Gasthuis, Noordwest Ziekenhuisgroep, IJsselland Ziekenhuis and Zuyderland MC (for pragmatic reasons); *and*
- were approached for study participation during their hospital admission, according to the patient dossier.

#### **8.4 Withdrawal of Individual Subjects**

Patients can withdraw from the study at any time for any reason without any consequences. The investigators or the medical staff can decide to withdraw a participant from the study for urgent medical reasons. In some cases, there may be exclusion criteria, which become apparent after inclusion. If this is the case, the patient might be withdrawn from the study; the responsible physician and investigators will decide this.

#### **8.5 Replacement of Individual Subjects after Withdrawal**

Individual subjects will not be replaced after withdrawal. There is no need to replace a patient that has withdrawn. In our sample calculation we anticipated a 10% rate of withdrawal for several reasons.

#### **8.6 Follow-up of subjects withdrawn from treatment**

Subjects withdrawn from the study will have the usual follow-up for patients operated for appendicitis. In most cases patients will be seen once after discharge in the outpatient clinic. After withdrawal patients will be included in the non-participants analysis, unless the reason for withdrawal was not meeting eligibility criteria (after all).

#### **8.7 Premature termination of the study**

The safety and feasibility of this trial depend on three main factors, namely:

- acceptable rate of mortality (90-day) in the intervention group (as compared to the control group)
- acceptable rate of serious postoperative complications (Clavien-Dindo class  $\geq 3$ ) in the intervention group (as compared to the control group)
- sufficient progress of inclusion of patients in the trial

Shortening duration of postoperative antibiotic treatment should not result in a significant increase of serious complications in need of invasive treatment and/or leading to Intensive Care admission or even death. An independent safety committee (DSMB) will be assembled to monitor trial safety and progress (See 9.5 Data Safety Monitoring Board), with special focus on imbalance between the two trial arms in 90-day mortality, serious postoperative complications. There will be two planned formal interim analyses: after the first 266 included patients have completed follow-up and after 666 have completed follow-up. Safety analyses will be performed using the alpha spending approach of O'Brien and Fleming. Suggested stopping guidelines will be a  $p < 0.000014$  at the first interim analysis and  $p < 0.009130$  at the second interim analysis for differences in 90-day mortality or serious postoperative complications between the trial arms. The final safety analyses will be performed with a significance level of 0.040855.

The DSMB will notify the coordinating- and principal investigators if the conditions of the stopping rules have been reached. The steering committee will decide on the continuation of the trial. If the trial steering committee decides to terminate the study prematurely, all participating centers will be notified immediately and further inclusion will be stopped. In case of premature termination, participants will not undergo any further research-related treatment and will instead receive the standard local treatment.

An extensive analysis will follow premature termination, regarding the encountered serious adverse events. The accredited METC will be notified within 15 days, including the reasons for the premature termination

## **9. SAFETY REPORTING**

### **9.1 Section 10 WMO event**

In accordance to section 10, subsection 1, of the WMO, the sponsor will inform the subjects and the reviewing accredited METC if anything occurs, due to which it appears the disadvantages of participation may be significantly greater than foreseen in the research proposal. In this case the study will be suspended pending further review by the accredited METC, except insofar as suspension would jeopardize the subjects' health. The sponsor will take care that all subjects are kept informed.

### **9.2 AEs, SAEs and SUSARs**

#### **9.2.1 Adverse events (AEs)**

Adverse events are defined as any undesirable experience occurring to a subject during the study, related to the experimental intervention. Undesirable experiences that are present irrespective of the study treatment are not considered adverse events in this trial. All adverse events reported spontaneously by the subject or observed by the investigator or his/her staff will be recorded (including postoperative complications) from the day of randomization until the end of follow-up. AEs are under responsibility of the investigators in participating centers.

#### **9.2.2 Serious adverse events (SAEs)**

A serious adverse event is any untoward medical occurrence or effect that at any dose:

- results in death;
- is life-threatening (at the time of the event);
- requires hospitalization or prolongation of existing inpatients' hospitalization;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect;
- any other important medical event that may not result in any of the outcomes listed above due to medical or surgical intervention but could have been, based upon appropriate judgement by the investigator.

The following events are not considered SAEs:

- Elective hospitalization (for pre-existent, concomitant disease) or hospitalization not related to serious adverse events (e.g. prolonging of stay to allow time for the home-situation to be prepared)
- Events and complications that are unrelated to the experimental study intervention (i.e. ileus, urinary tract infections).

The local investigator will assess causality and decide whether or not a serious adverse event is related to the study. If there is even the slightest evidence to suggest a causal relationship the event should be considered an SAE.

The sponsor will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

SAEs are under responsibility of the investigators in participating centers. Investigators in the participating centers will report the adverse event within 5 days to the coordinating investigator.

The investigator will report all SAEs to the sponsor without undue delay after obtaining knowledge of the events, except for the following SAEs which are by nature associated with complex appendicitis as progression or complication of disease:

- intra-abdominal abscesses, that require additional treatment and/or hospitalization, but are not life-threatening.
- surgical site infections, that require additional treatment and/or hospitalization, but are not life-threatening.

These SAEs will be recorded in an overview to be submitted to the METC periodically, once every half year. Excluding them from expedited reporting to the METC through *ToetsingOnline* is justified, as there will be a DSMB monitoring safety at regular intervals, which will include analysis of all postoperative complications. As soon as these SAEs advance to a life-threatening complication and/or result in mortality, they do have to be reported without undue delay.

### **9.2.3 Suspected unexpected serious adverse reactions (SUSARs)**

Adverse reactions are all untoward and unintended responses to a non-investigational product related to any dose administered.

Unexpected adverse reactions are SUSARs if the following three conditions are met:

1. the event must be serious (see paragraph 9.2.2);
2. there must be a certain degree of probability that the event is a harmful and an undesirable reaction to the medicinal product under investigation, regardless of the administered dose;
3. the adverse reaction must be unexpected, that is to say, the nature and severity of the adverse reaction are not in agreement with the product information as recorded in the Summary of Product Characteristics (SPC).

The sponsor will report expedited the following SUSARs through the web portal *ToetsingOnline* to the METC:

- SUSARs that have arisen in the clinical trial that was assessed by the METC;
- SUSARs that have arisen in other clinical trials of the same sponsor and with the same medicinal product, and that could have consequences for the safety of the subjects involved in the clinical trial that was assessed by the METC.

The remaining SUSARs are recorded in an overview list (line-listing) that will be submitted once every half year to the METC. This line-listing provides an overview of all SUSARs from the study medicine, accompanied by a brief report highlighting the main points of concern.

The expedited reporting of SUSARs through the web portal *ToetsingOnline* is sufficient as notification to the competent authority.

The sponsor will report expedited all SUSARs to the competent authorities in other Member States, according to the requirements of the Member States.

The expedited reporting will occur not later than 15 days after the investigator has first knowledge of the adverse reactions. For fatal or life threatening cases the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report.

SUSARS are under responsibility of the investigators in participating centers. Investigators in the participating centers will report the adverse event within 5 days to the coordinating investigator.

### 9.3 Annual safety report

In addition to the expedited reporting of SUSARs, the sponsor will submit, once a year throughout the clinical trial, a safety report to the accredited METC, competent authority, and competent authorities of the concerned Member States.

This safety report consists of:

- a list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported serious adverse reactions, ordered by organ system, per study;
- a report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation.

### 9.4 Follow-up of adverse events

All adverse events will be followed until they have abated or a stable situation has been reached. Depending on the event, follow-up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist. SAEs need to be reported till end of study within the Netherlands, as defined in the protocol.

### 9.5 Data Safety Monitoring Board (DSMB)

An independent data and safety committee (DSMB) will be established to perform on-going safety surveillance and assess safety and efficacy data and the stopping guideline as described at 8.7. The stopping rule will be tested at two planned safety interim analyses: after the first 266 included patients have completed follow-up and after 666 have done so.

The DSMB will consist of one epidemiologist/statistician, a surgeon and a microbiologist (to be appointed after submission of this protocol) from the Erasmus MC, all of whom are unrelated to this study and have no conflict of interest with the coordinating investigator of the study. They will examine safety parameters at regular intervals and monitor whether stopping rules have been reached (see section 8.7 Premature termination of the study). They will also continuously review whether adverse events (AEs) as reported by the participating centers fulfill the criteria of 'serious complication' as defined in the stopping rules. They will make recommendations regarding study continuation, termination, or modifications to the study design. Recommendations of the DSMB will be sent to the steering committee. Should the steering committee decide not to fully implement the advice of the DSMB, the then

sponsor will send the advice will be forwarded to the reviewing METC, including a note to substantiate why (part of) the advice of the DSMB will not be followed.

The DSMB roles, responsibilities, meetings and logistics are outlined in greater detail in Attachment K5: the APPIC trial DSMB Charter.

## 10. STATISTICAL ANALYSIS

### 10.1 Primary study parameter(s)

The primary endpoint is a composite endpoint of infectious complications related to appendectomy and mortality, as defined in chapter 2 and 8. Non-inferiority of 48 hours of (the intervention group) versus five days (the control group) of postoperative intravenous antibiotic treatment in terms of the primary endpoint rate will be assessed using a one-sided 97.5% confidence interval for the effect of the study group (absolute risk difference). This confidence interval will be adjusted for the effects of severity of disease and age (as one categorical covariate), using the method proposed by Klingenberg (83, 100). Non-inferiority will be established if the upper limit of this confidence interval for the absolute risk difference is lower than 7.5%. Based on the non-inferiority design, both per-protocol and intention-to-treat analyses will be performed.

In a secondary analysis, logistic regression analysis will be performed to identify predictors of the composite primary endpoint. The independent variables in this model will include treatment group and also age, sex, surgical approach (open versus laparoscopic), severity of appendicitis, ASA score and center, as well as significant interaction effects of these independent variables with treatment group.

### 10.2 Secondary study parameter(s)

General patient characteristics will be compared between the intervention group and the control group with the independent Student's t-test or the Mann-Whitney test in case of continuous outcome variables and the Chi-square or Fisher's exact test in case of categorical outcome variables where appropriate. The following secondary endpoints will be compared between the trial arms using linear regression for continuous outcomes and logistic regression for dichotomous outcomes, with adjustment for the effects of age, sex, surgical approach (open versus laparoscopic), severity of appendicitis, ASA score and center: mortality, intra-abdominal abscess, superficial and/or deep surgical site infection, duration and total doses of postoperative antibiotic treatment, re-start of antibiotics, hospital stay in hours from the operation, time to reach discharge criteria in hours from the operation, emergency department visits and readmission rate and adverse events on antibiotics. In case of non-normally distributed continuous outcomes, appropriate transformation of these outcomes will be applied. A two-sided significance level of 0.05 will be used for all secondary analyses.

*Analysis of cost-effectiveness*

- Economic evaluation: a calculation will be made of the incremental health care costs and societal costs respectively per additional/avoided complication of short versus longer postoperative antibiotic use. Using non-parametric bootstrapping (randomly drawing 5000 observations with replacement from the patient sample), the degree of uncertainty for both costs and health effects and the cost-effectiveness ratio will be depicted in a cost-effectiveness plane. In addition an acceptability curve will be drawn, which indicates the probability that the short antibiotic course has lower incremental costs per additional/avoided complication.
- Cost-analysis: Patients' hospital consumption (surgery, use of antibiotics, laboratory, inpatient days, post-operative outpatient visit and complications (including emergency department visits, readmission, re-interventions, laboratory and inpatient days)) will be registered in the clinical registration form. Productivity costs due to absence from work for patients aged 18 and older will be measured and valued by means of the validated Productivity Cost Questionnaire ([www.imta.nl](http://www.imta.nl)), completed during the postoperative outpatient visit. For patients under 18, the number of days absent from school will be used. The costs per unit of medical consumption and per day of work absence will be estimated, using information from the recently revised Dutch costing Manual for economic evaluation of health care ([www.zorginstituut.nl](http://www.zorginstituut.nl)). Costs will be reported in euros for the year 2017. An attempt will be made to estimate the possible reduction in costs of antibiotic resistance, in case the short course of antibiotics is non-inferior.
- Budget impact analysis: An estimate of the budgetary impact for the Netherlands will be made, comparing the results (especially due to changes in length of hospital stay and complication rates) for the short antibiotic course with recent evidence of care as usual in the Netherlands. The current tariffs and DBC/DOT-fees will be used.

**10.3 Other study parameters**

All preoperative, perioperative and postoperative parameters as listed in 8.1.3 will be compared between the intervention group and the control group using the same statistical tests as described for secondary parameters at 10.2, with a two-sided significance level of 0.05 as well.

*Non-participants analysis*

Data on study parameters collected from non-participants will be compared to data from the APPIC trial population. Again, the same statistical tests as described for secondary parameters at 10.2 will be used, with a two-sided significance level of 0.05.

**10.4 Interim analysis**

Two interim analyses are planned to assess the safety stopping rule: after the first 266 included patients have completed follow-up and after 666 have. Safety analyses will be performed using the alpha spending approach per O'Brien and Fleming. Suggested stopping guidelines will be a p-value  $< 0.000014$  at the first interim analysis and  $p < 0.009130$  at the second for differences in 90-day mortality or serious postoperative complications between the trial arms. The final safety analyses will be performed with a significance level of 0.040855. An independent statistician, blinded for treatment allocation, will perform the safety-analyses and report to the DSMB. The DSMB will discuss the results of the safety-analyses and give advice to the steering committee as described at 8.7 and 9.5.

No interim analysis on efficacy will be performed nor will the study be analyzed for futility.

## 11. ETHICAL CONSIDERATIONS

### 11.1 Regulation statement

This study will be conducted according to the principles of the Declaration of Helsinki (version 9, 64th WMA General Assembly, Fortaleza, Brazil, October 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO) and ICP-GCP.

### 11.2 Recruitment and consent

Patients will be recruited for the RCT when they are admitted to the Emergency Room or hospital. The responsible physician informs the patient or parent(s)/caregiver(s)/legal representative about the clinical condition of the patient and either recruits the patient and/or introduces the investigator. It is the responsibility of the investigators to provide the patients with detailed information, both orally and in writing, about the aims and design of the study, as well as the study procedures involved. The patients will have the opportunity to ask all possible questions and receive additional information throughout enrollment in this study. They will also receive a patient information letter and an informed consent form. In addition to the information given orally and in writing, patients may be referred to an informative animated (online) video regarding the trial. Participants will be given as much time as they desire to consider their decision, until 24 hours after appendectomy at the latest.

#### *Non-participants analysis*

Owing to the observational nature of the non-participants analysis, no patient consent is needed from them according to the WMO. In 6 participating centers non-participants will once receive a short questionnaire. Apart from that, the non-participants analysis consists solely of electronic patient file research, of a limited amount of non-sensitive data. Criteria for waiving patient consent requirement on grounds of the AVG (article 24) and WGBO (article 458) are met as well:

- Explicit consent from all patients could only be obtained with disproportionate efforts due to the large number of patients and time period. It is estimated that over 900 patients undergo appendectomy for complex appendicitis annually in the participating centers. Recruitment started in May 2017 and is expected to be completed in the 2<sup>nd</sup> half of 2020. As from May 2019 a 15<sup>th</sup> center will initiate recruitment. It would take disproportionate time and effort to reach all non-participants (estimated > 1500) in order to obtain their consent. Moreover, this may introduce selection bias, as a certain type of patient (i.e.

elderly) may be overrepresented in the sample answering to a request for permission via post.

- This sub study serves the general public health interest. Acute appendicitis is a highly prevalent disease among both adults and children. Over 14.000 patients annually undergo appendectomy in the Netherlands, many of which are treated with antibiotics postoperatively. With the growing worldwide issue of antimicrobial resistance, it is key to battle antibiotic overtreatment. To further strengthen the impact of the APPIC trial, it is important to assess the external validity of the study. That is what this observational non-participants analysis contributes to.
- To assess the external validity and generalizability it is necessary to process the patient data as proposed in order to be able to compare the study participants to the non-participants: extracting a limited number of patient characteristics from the individual patient files in a pseudonymized manner. No more personal data than strictly necessary will be processed.
- This sub study is entirely aimed at analysing data that are already present in the electronic patient files. There is no psychological burden for patients and their privacy will not be disproportionately harmed. Data will be handled in encoded form and redirection will be reasonably prevented. Complete anonymization is impossible since there must remain a possibility for demonstrating correctness of the data. The key between the study code and the individual patient will be safeguarded by the principal investigator in a secure environment where only authorized research team members may access it. The sub study data will be stored in OpenClinica, which meets all safety requirement as set and tested by the information security department of the Erasmus MC.
- If a patient has explicitly objected to use of his/her personal data no data will be collected or processed from this patient. If such an objection is not traceable (in the patient files), this will be considered no objection.

### **11.3 Objection by minors or incapacitated subjects**

Minors and/or incapacitated adults participate in this therapeutic research. Minors and/or incapacitated adults will be withdrawn from the study in case of any resist.

### **11.4 Benefits and risks assessment, group relatedness**

The present study will try to obtain a clear view of the effects of antibiotic use after appendectomy for complex appendicitis in terms of postoperative complications. Treatment of complex acute appendicitis with these antibiotics is common practice in the Netherlands.

They have been widely used for a long time already and toxicity and possible side effects are well documented. Therefore no extra risks are associated with the medicinal products.

Participating in this study has no personal benefit for participants, except for patients in the intervention group in terms of patient comfort due to shorter intravenous treatment resulting in a possibly shorter hospital stay. The long-term benefits of this study may be less antibiotic use, less antibiotic overtreatment and resistance, shorter hospitalization of patients and lower associated hospital costs.

The risk of reducing antibiotic treatment in the intervention group in terms of a possibly higher rate of infectious complications is considered low. To closely monitor clinically important complications an independent data safety monitoring board (DSMB) will evaluate at regular intervals. No extra burden is associated with trial-participation in the context of no extra number and amount of blood samples, no extra number of site visits, no other physical examination or tests are necessary. The only difference compared to standard treatment is that four weeks after appendectomy patients will be asked to complete and hand in a questionnaire (Productivity Cost Questionnaire). And 90 days after appendectomy a final follow-up by telephone will take place.

### **11.5 Compensation for injury**

The sponsor/investigator has a liability insurance that is in accordance with the legal requirements in The Netherlands (Article 7 WMO and the Measure regarding Compulsory Insurance for Clinical Research in Humans of 23th June 2003). This insurance provides cover for damage to research participants through injury or death caused by the study.

The following amounts are paid in case of injury or death caused by the study:

1. A maximum of €450.000 for death or injury for each subject who participates in the research.
2. A maximum of €3.500.000 for death or injury for all subjects who participate in the research.
3. €5.000.000 for the total damage incurred by the organization for all damage disclosed by scientific research for the sponsor as 'verrichter' in the meaning of said Act in each year of insurance coverage.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

**11.6 Incentives (if applicable)**

Not applicable.

## 12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

### 12.1 Handling and storage of data and documents

Research data will be stored in an ALEA database. The ALEA database system was tested and validated by the International Society for Pharmaceutical Engineering (ISPE) GAMP 5 Good Practice Guide (the GAMP 5: A risk-based approach to compliant GxP computerized systems). It was also tested and validated by the Clinical Trial Center of the Erasmus MC. Moreover, the Chief Information Security Officer of the Erasmus MC (drs. Jan Willem Schoenmaker) had approved it for use in randomized trials in the Erasmus MC.

Data will be handled confidentially. Data will be saved for 15 years. Upon inclusion into this study, each patient will be assigned a study number. This study number will be listed on all study related documentation. In this study, no personal documents will be listed. The key to the code will be stored in a separate document. When it is necessary to trace data to an individual subject, a subject identification code list will be used to link the data to the subject. The code will not be based on the patient's initials and birth-date. The key to the patient study number is safeguarded by the local investigator.

The handling of personal data is in compliance with the Dutch Data Protection Act (in Dutch: 'Algemene Verordening Gegevensbescherming, AVG).

### 12.2 Monitoring and Quality Assurance

Monitoring and quality assurance will be performed by an independent company (Clinical Trial Centre of the Erasmus MC). This will take place at least once every year during the period of enrolling patients. Monitoring will be performed according to 'Attachment A' of the Monitoring plan (see Attachment K6 for details).

### 12.3 Amendments

Amendments are changes made to the research after a favorable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favorable opinion.

A 'substantial amendment' is defined as an amendment to the terms of the METC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;

- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments will be notified to the METC and to the competent authority.

Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor. Examples of non-substantial amendments are typing errors and administrative changes like changes in name, telephone numbers and others contact details of involved persons mentioned in the submitted study documentation.

#### **12.4 Annual progress report**

The sponsor/coordinating investigators will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, number of subjects included and numbers of subjects that have completed the trial, serious adverse events / serious adverse reactions, other problems and amendments.

#### **12.5 Temporary halt and (prematurely) end of study report**

The sponsor will notify the accredited METC and the competent authority of the end of the study within a period of 90 days. The end of the study is defined as the last patient's last visit. The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited METC and the competent authority within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC and the Competent Authority.

#### **12.6 Public Disclosure and Publication Policy**

The coordinating investigator is responsible for the public disclosure and publication of the research data.

The protocol and the (final) results of the study will be summarized in a report / article and will be submitted for publication in a medical journal. Also, all participating patients or their family will receive a layman's summary of the (final) results of the study.

This clinical trial was registered in the Netherlands Trial Register (NTR) on December 12th 2016 with NTR ID 6128 (old) and NL ID NL5946 (new)..

## 13. STRUCTURED RISK ANALYSIS

### 13.1 Potential issues of concern NA

### 13.2 Synthesis

Chapter 13.1 is skipped, because in this trial registered medicinal products will be used for the indication they are registered for, not in combination with other products. As stated before, both cefuroxime/metronidazole and ceftriaxone/metronidazole have been widely used for a long time and toxicity and possible side effects are well documented. Chosen route of administration and dosages are standard practice. Therefore in this trial no extra risk is associated with the medicinal products.

Goal of the present study is to investigate whether stopping antibiotic treatment early, after 48 hours, is safe and effective as compared to standard treatment of five days. To reduce the risk, severely ill patients are excluded from this study: patients with (suspected) severe sepsis preoperatively and/or inadequate source control cannot participate (See 4.3 Exclusion criteria). A possible risk of antibiotic undertreatment remains for the participants in the intervention group of this study: they might have a higher risk of infectious complications following appendectomy as compared to patients in the control group. This is an acceptable risk because:

- existing literature shows promising results in favor of shorter antibiotic duration, not resulting in a higher rate of complications (See Chapter 1)
- infectious complications that may arise can be detected and treated well, and have minimum consequences in terms of severe morbidity and/or mortality
- a safety committee (DSMB) will be established that will continuously monitor and review safety parameters

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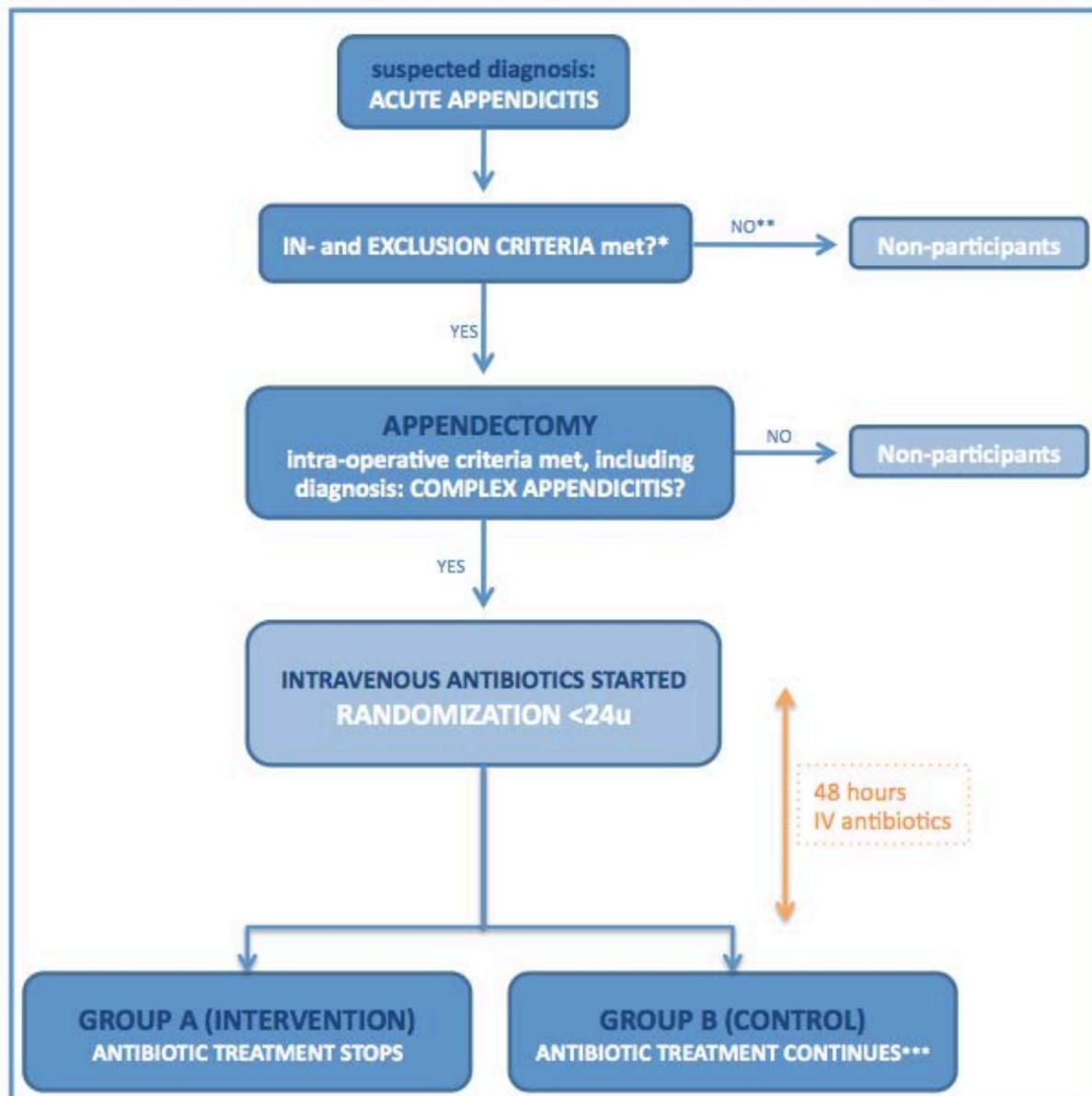
**APPENDIX I: Overview of guidelines on antibiotics for appendicitis**Table 1. Current guidelines on perioperative antibiotic treatment for simple appendicitis

Guidelines	Duration	Antibiotic agent
<u>NVvH (34)</u> 2010	One single dose	Not mentioned
<u>SWAB (33)</u>	One single dose	Cefazolin and metronidazole, second choice amoxicillin clavulanic acid
<u>SIS/IDSA (29)</u> 2010	Discontinued within 24 hours	Cefazolin, cefuroxime, ceftriaxone, cefotaxime, ciprofloxacin, or levofloxacin, each in combination with metronidazole (in paediatric patients: ceftriaxone, cefotaxime, cefepime, or ceftazidime, each in combination with metronidazole; gentamicin or tobramycin, each in combination with metronidazole or clindamycin, and with or without ampicillin)

Table 2. Current guidelines on postoperative antibiotic treatment for complex appendicitis

Guidelines	Duration	Antibiotic agent	Switch to oral agent
<u>NVvH (34)</u> 2010	3-7 days	Should be effective against both aerobic and anaerobic bacteria (not otherwise specified)	May be considered after 48 hours, when oral intake is resumed
<u>SWAB (33)</u>	5-14 days	Ceftriaxone or cefuroxime in combination with metronidazole, amoxicillin clavulanic acid. Optional, aminoglycoside could be given before the cultures are know	Not mentioned
<u>SIS/IDSA (29)</u> 2010	4-7 days	Cefazolin, cefuroxime, ceftriaxone, cefotaxime, ciprofloxacin, or levofloxacin, each in combination with metronidazole (in paediatric patients: ceftriaxone, cefotaxime, cefepime, or ceftazidime, each in combination with metronidazole; gentamicin or tobramycin, each in combination with metronidazole or clindamycin, and with or without ampicillin)	Moxifloxacin, ciprofloxacin or levofloxacin plus metronidazole, an oral cephalosporin plus metronidazole, or amoxicillin-clavulanic acid
<u>WSES (39)</u> 2016	3 – 5 days	Broad-spectrum antibiotics (not otherwise specified)	Not mentioned

## APPENDIX II: Trial flowchart

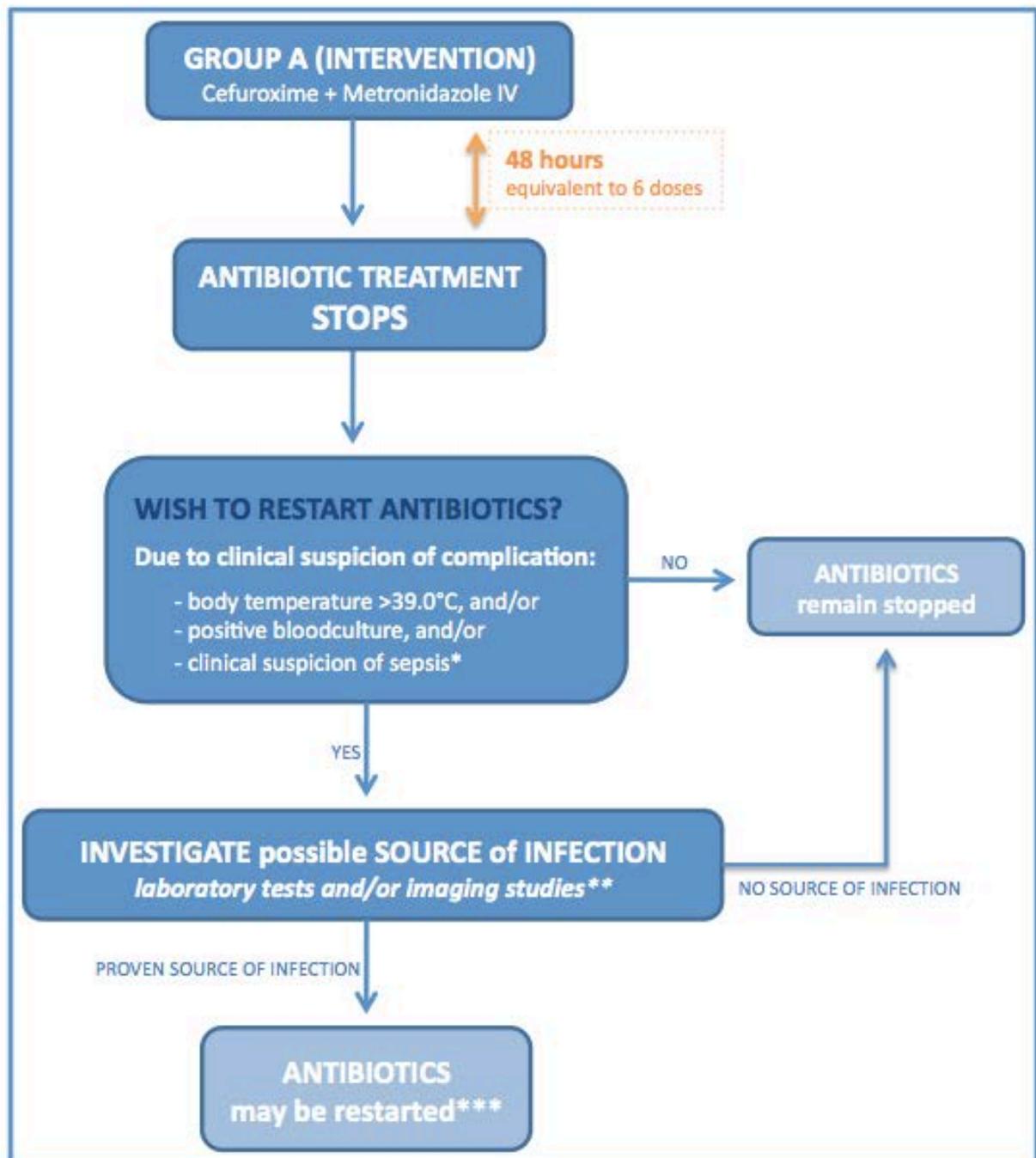


\* All except intra-operative criteria regarding severity of appendicitis;

\*\* If the patient hasn't been able to give informed consent prior to appendectomy, this may still be acquired postoperatively, as long as inclusion and randomization takes place within 24 hours.

\*\*\* Intravenous antibiotic treatment continues for three more days to complete five days in total.

## APPENDIX III: Decision algorithm for restarting antibiotics



\* Two or more of the following: body temperature  $<36.0^{\circ}\text{C}$  or  $>38.0^{\circ}\text{C}$ ; heart rate  $> 100\text{bpm}$ ; respiratory rate  $> 20/\text{min}$ ; WBC  $<4 \times 10^9$  or  $>12 \times 10^9$  cells/L.

\*\* As appropriate according to Dutch guidelines and local hospital protocols.

\*\*\* Depending on source of infection different antibiotic regimes may be indicated and/or invasive source control therapy, such as percutaneous drainage of an abscess.

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