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 ≥ 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.