A multicenter randomized clinical trial investigating the cost-effectiveness of treatment strategies with or without antibiotics for uncomplicated acute diverticulitis

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	**ABR form (General Assessment and Registration form) is the application form that is required for submission to the accredited Ethics Committee (ABR = Algemene Beoordeling en Registratie)**
AE	**Adverse Event**
AR	**Adverse Reaction**
CA	**Competent Authority**
CCMO	**Central Committee on Research Involving Human Subjects**
CV	**Curriculum Vitae**
DSMB	**Data Safety Monitoring Board**
EU	**European Union**
EudraCT	**European drug regulatory affairs Clinical Trials GCP Good Clinical Practice**
IB	**Investigator's Brochure**
IC	**Informed Consent**
IMP	**Investigational Medicinal Product**
IMPD	**Investigational Medicinal Product Dossier**
METC	**Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)**
(S)AE	**Serious Adverse Event**
SPC	**Summary of Product Characteristics (in Dutch: officiële productinfomatie IB1-tekst)**
Sponsor	**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.**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
Wbp	**Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)**
WMO	**Medical Research Involving Human Subjects Act (Wet Medisch-wetenschappelijk Onderzoek met Mensen**

SUMMARY

Rationale: The prevalence of colonic diverticular disease is increasing in Western countries. Approximately 10 to 25% of patients with diverticular disease will eventually develop an episode of acute diverticulitis. Currently conservative treatment often includes antibiotic therapy. This advice lacks sound evidence and is merely based on experts' opinion. An old clinical dogma is being clarified with this randomized trial.

Objective: Primary objective is to evaluate whether or not using antibiotics reduces to time to full recovery of an attack of uncomplicated (mild) diverticulitis. Secondary objectives are to evaluate complications, quality of life, readmission rate, recurrence rate, medical and non-medical costs, and antibiotic resistance/sensitivity in both groups.

Study design: A randomized, open label, multicenter clinical trial comparing treatment of acute uncomplicated diverticulitis with antibiotics to observation and supportive care alone.

Study population: Patients 18 years or older are eligible for inclusion if they have a diagnosis of acute uncomplicated diverticulitis as demonstrated by imaging. Only patients with stages 1a and 1b according to Hinchey's classification or "mild" diverticulitis according to the Ambrosetti criteria are included.

Intervention: Conservative strategy with antibiotics: supportive measures and at least 48 hours of intravenous antibiotics (and therefore admittance to the hospital) and subsequently switch to oral antibiotics if tolerated (total duration of 10 days).

Control: Liberal strategy without antibiotics: supportive measures only. Observation and oral intake as tolerated. Admittance only if discharge criteria are not met on presentation.

Main study parameters/endpoints: The primary endpoint is time-to-recovery with a 6-month follow-up period. Secondary endpoints are occurrence of complicated diverticulitis requiring surgery or percutaneous treatment, morbidity, health related quality of life, readmission rate, recurrence rate, medical and non-medical costs, and antibiotic resistance/sensitivity.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Both treatment regimens in this study are commonly used in the Netherlands and are considered standard of care. The investigational products used in the study have been widely used for a long time already and toxicity and possible side effects are well documented. Treatment of uncomplicated diverticulitis with these antibiotics is common practise in most countries. The risk of omitting antibiotics is probably very low but an independent safety commission closely monitors clinical important complications after every 25 patients included. The only difference compared to standard treatment is patients have to fill out three quality of life questionnaires on admission and after 3, 6, 12 and 24 months, keep a patient diary when an outpatient until full recovery and submit feces for culture, so the additional burden for participants is considered minimal.

1. INTRODUCTION AND RATIONALE

Diverticulosis is an anatomical description indicating the presence of one or more diverticula. Diverticular disease covers the whole spectrum of asymptomatic and symptomatic disease associated with colonic diverticula. Symptomatic uncomplicated diverticulosis is associated with mild symptoms, usually abdominal pain and/or change in bowel habit, but without clinical features of inflammation. Diverticulitis is diverticular disease with profound clinical symptoms and evidence of inflammation. Complicated diverticulitis means perforation, abscess, fistula, bleeding or stricture, usually needing surgical or percutaneous intervention. (1)

In Western countries colonic diverticulosis predominantly affects the sigmoid and distal descending colon. Diverticulosis of the right colon, without disease on the left side, is viewed as a separate condition. Right-sided diverticular disease is more common in Asia, where the Western type is uncommon, and visa versa. In the present study we will investigate left-sided diverticulitis. Prevalence of diverticular disease increases with age, from less than 10% in people younger than age 40 to 50–66% in octogenarians, with similar frequency in men and women. Approximately three quarters of patients with diverticulosis remain asymptomatic throughout their lifetime. Asymptomatic disease is often an incidental finding during imaging or endoscopy for suspicion of colonic disorders. Of the 25% of patients who develop symptomatic diverticular disease, approximately three quarters develop diverticulitis (2). Of all patients with diverticulitis, 75% have mild acute disease and 25% develop complicated disease. (2,3) All and all about 5% of patients with diverticulosis will experience an episode of complicated diverticulitis.

The cause of colonic diverticular disease has not yet been conclusively established. Factors that have been associated with an increased risk of diverticular disease include low dietary fibre intake, physical inactivity, constipation, obesity, smoking, and treatment with nonsteroidal anti-inflammatory drugs. (4)
Although much has been learned about the development of the diverticula, less is known about the pathogenesis of diverticular inflammation. The process by which diverticulitis arises is thought to be comparable to that of appendicitis, with a diverticulum becoming obstructed by inspissated stool in its neck. This faecolith abrades the mucosa of the sac, causing inflammation and expansion of bacterial flora, with diminished venous outflow and localised ischemia. (1)

For establishing the diagnosis, when the combination of the patient's history, signs and symptoms during physical examination and blood testing raise the possibility of diverticulitis,

additional radiological imaging is necessary. CT scanning is recommended as initial radiological examination. Although positive findings in ultrasound are equally accurate in the diagnosis of diverticulitis, CT has an advantage in excluding alternative diagnoses and visualising complications of acute diverticulitis needing intervention. Our group has evaluated test accuracy for ultrasound and CT, with sensitivity as high as 90% and specificity of up to 99% for CT (5). The severity of diverticulitis is often graded with the use of Hinchey's (6) or Ambrosetti's (7) criteria based on CT imaging (table 1). These classification systems are descripitive and do not take into account the effects of coexisting conditions on disease severity or outcome (8).

Conservative treatment of mild diverticulitis usually includes in-patient care with careful observation, restriction of oral intake, symptomatic pain relief, intravenous fluids, and most patients receive antibiotic therapy. The majority of the mild diverticulitis patients improve with these conservative measures; only 15-30% of the patients need percutaneous and/or operative treatment for disease progression and/or complications. (1)

It is, however, uncertain whether patients with acute diverticulitis benefit from antibiotics, since evidence from prospective studies or randomized trials is lacking. In a recent review antibiotics are considered mandatory in the treatment of mild diverticulitis. (1) Five professional organisations have issued formal guidelines concerning to use of antibiotics in uncomplicated diverticulitis. All guidelines advice the use of antibiotics. (9-13) This advice lacks evidence and is based on experts' opinion only. Our group recently conducted a systematic review. (14) There is some evidence that oral antibiotics might be as effective as intravenous antibiotics. (15) No firm conclusions can be drawn as to what antibiotics should be used. (16-17) In 2008 Hjern et al concluded that the use of antibiotics shows no significant benefit in the treatment of mild diverticulitis (18). However, this study was hampered by selection bias due to its retrospective design and small patient groups. Until now there is no clinical randomised trial dealing with this treatment dilemma of acute uncomplicated diverticulitis. A recent survey among gastroenterologists and surgeons in the Netherlands shows that 90% of both does not routinely use antibiotics in the treatment of uncomplicated diverticulitis. (19)

Anaerobes are the most commonly isolated organisms in acute diverticulitis. Gram-negative aerobes, especially Escherichia coli, and facultative gram-positive bacteria, such as streptococci, are often cultured as well. Therefore, broad-spectrum antibiotics are advised. Patients should start with intravenous antibiotics and after improvement within 2-4 days oral antibiotics are continued to a complete 7-10 day treatment. (1) In the Netherlands, the Dutch

Antibiotic Policy Committe (SWAB (Stichting Werkgroep Antibiotica Beleid)) considers antibiotics not primarily indicated in the treatment of uncomplicated diverticulitis. (20) (Table 2) Adverse effects of the use of antibiotics are well-known, such as allergic reactions, development of antibiotic resistance of bacterial species, and various side-effects. The frequency of toxicodermia is 7-8% with amoxicillin, allergic reactions are accounted for in 1% of the patients and the incidence of anaphylactic shock is between 0.01-0.04% with the use of penicillin. (21) With the use of other antibiotics allergic reactions are less but there is a much higher incidence of nephro-toxicity. Over the last decade efforts have been made to minimize the use of antibiotics in various fields in clinical medicine. Examples are appendiceal mass, acute cholecystitis, and this is also true for community-acquired infections, such as acute otitis media and maxillary sinusitus. (22-23) Resistance to antibiotics is a major public-health problem and antibiotic use is being increasingly recognized as the main selective pressure driving this resistance. (24)

The potential benefits of a more liberal treatment strategy for acute diverticulitis include shorter duration of hospital admission, cost reduction, less antibiotic resistance development and side effects. The potential harms of the liberal strategy include higher readmission rates, delayed treatment of infectious complications, higher treatment failure rate, more complicated disease and extra costs related to additional procedures. The actual balance between clinical effects and costs for both strategies is not known. Uncomplicated diverticulitis usually is a self-limiting disease and accounts for almost 90% of the patients with diverticulitis. Our study design reflects current clinical practice in which two different approaches are commonly applied next to each other and are both considered standard of care. This trial will clarify an old clinical dogma.

2. OBJECTIVES

Primary Objective

Our main goal is to establish whether antibiotics are necessary in the primary treatment of acute mild diverticulitis, or whether a more liberal strategy without initial antibiotics is equally effective in achieving recovery but is associated with changes in quality of life and lower costs.
In daily practice there is an ongoing discussion about the relative benefits and disadvantages of a more conservative treatment strategy embracing the use of intravenous antibiotics. This latter strategy is strictly in-hospital. All these conservative measures lead to a considerable duration of hospital stay (Prismant data: median 7 days). A more liberal strategy, without antibiotics and without the strict requirement of hospital admission, may lead to a shorter hospital stay and reduced costs without compromising outcome.
Our hypothesis is that in the treatment of uncomplicated (mild) acute diverticulitis, a liberal strategy treatment without antibiotics is a more cost-effective approach than conservative treatment with hospital admission and antibiotics with respect to time-to-recovery as primary outcome.

Secondary Objective(s)

To evaluate complications, quality of life, readmission rate, recurrence rate, medical and non-medical costs, and antibiotic resistance/sensitivity in both groups

3. STUDY DESIGN

The proposed study is a randomized, open label, clinical trial comparing two treatment strategies for uncomplicated (mild) acute diverticulitis. Patients will be randomly allocated to A) treatment with antibiotics or B) no antibiotics, observation and supportive care only. (See flowchart fig 3.)
The study is multicenter with 2 academic and 11 teaching hospitals have already indicated that they are willing to participate pending ethical approval. The proposed starting date is 31-11-2009 and accrual will take place for 24 months.

This trial is an example of a strategy or management trial where there is an initial difference in treatment, but many other care decisions will follow given the complex interaction between initial treatment and the underlying disease. Masking of treatment is not only difficult to achieve, but also undesirable because good clinical decision-making requires knowledge of the specific interventions that have been given. (For instance, the decision to start antibiotic treatment in the strategy without initial antibiotic therapy). Valid outcome assessment is critical in strategy trials and a mixture of objective and subjective outcomes is needed as we have in our trial. Furthermore, outcome criteria should be specified in advance and an outcome event (adjudication) committee of experts will be installed that will judge based on all relevant clinical data of individual patients whether a specific outcome has occurred. These experts will be blinded for the allocated treatment strategy

4. STUDY POPULATION

4.1 Population (base)

Patients 18 years or older with uncomplicated acute (left-sided) diverticulitis which is ultrasound or CT proven and who gave informed consent on first presentation.

The logistic requirements have been set out within the multicenter collaboration of the OPTIMA trial that has succeeded in including more than 1000 patients with abdominal pain in less than 2 years. The hospitals of the collaboration have been approached for patient inclusion. In the OPTIMA trial 12% of all patients presented with abdominal pain had CT proven diverticulitis. During the Diverticulitis Symposium 2008 in Delft 3 hospitals presented their data; on average they admitted 30 patients each year with acute diverticulitis primarily treated conservatively. A total 15 hospitals have committed to DIABOLO study participation, which theoretically includes 325 patients each year: AMC Amsterdam, OLVG Amsterdam, Lucas Andreas Hospital Amsterdam, Boven IJ Hospital Amsterdam, Tergooi Hospital, Gelre Hospitals Apeldoorn, Albert Schweitzer Hospital Dordrecht, Kennemer Hospital Haarlem, Maxima Hospital Veldhoven, VUMC Amsterdam, Meander Hospital Amersfoort, Spaarne Hospitals Hoofddorp, Rode Kruis Hospital Beverwijk, Amphia Hospital Breda and Ziekenhuisgroep Twente. To optimally secure patient accrual other hospitals have already been approached and their approval is awaited. An accrual period of 24 months should sufficient to include the needed number of patients also accounting for a one percent dropout rate.

4.2 Inclusion criteria

1. Only left-sided uncomplicated (mild) acute diverticulitis;
2. Clinical suspicion of acute diverticulitis. For acute diagnostic work-up: ultrasound or CT proven diverticulitis. In the case of diverticulitis-negative ultrasound in clinically suspected patients an intravenous contrast-enhanced CT scan is mandatory for confirmation of diverticulitis or exclusion of other pathology. CT for Hinchey/Ambrosetti classification (which is a CT-based classification system) is needed for all patients, but can be delayed 1 day in those with ultrasound diagnosis. Staging diverticultis is defined according the modified Hinchey/Ambrosetti staging, only stages 1a and 1b and "mild" diverticulitis (1a Confined pericoloc inflammation, 1b Confined small (smaller than 5cm) pericolic

abscess) are included. In the attachments we have added a flow chart, showing systematically the inclusion criteria and the following steps after inclusion;
3. All patients with informed consent.

4.3 Exclusion criteria

1. Previous radiological (ultrasound and/or CT) proven episode of diverticulitis;
2. US and/or CT suspicion of colonic cancer;
3. Inflammatory bowel disease (ulcerative colitis, Crohn's disease);
4. Hinchey stages 2, 3 and 4 or "severe" diverticulitis according to the Ambrosetti criteria, which require surgical or percutaneous treatment;
5. Other disease with expected survival of less than 6 months;
6. Contraindication for the use of the study medication (e.g. patients with advanced renal failure or allergy to all antibiotics used in this study);
7. Pregnancy, breastfeeding;
8. ASA (American Society of Anaesthesiologists) classification > III;
9. 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 long-term immunosuppressant use (such as corticosteroids in patients with rheumatoid arthritis));
10. Clinical suspicion of bacteraemia (i.e. sepsis);
11. The inability of reading/understanding and filling in the questionnaires;
12. Antibiotic use in the 4 weeks prior to inclusion.

4.4 Sample size calculation

This is a non-inferiority design: time-to-recovery must not be clinically relevant longer in the liberal strategy than in the conservative strategy. When this condition is fulfilled, the potential advantages of the liberal (non-antibiotic) strategy become dominant: patient well being when need of hospital admission can be avoided, less costs, less antibiotic resistance and other side effects. A difference in time-to-recovery of less than 5 days is considered non-inferior. The study must have the power to detect a difference in time-to-recovery of 5 days in a superiority design to reject the null hypothesis that there is no clinically significant difference in time-to-full-recovery. To reject the null hypothesis of a difference in time-to-recovery of 5 days or less (median time-to-recovery from 21 days

(based on the Prismant data of an average of 7 days admission and an assumed additional median 14-day out-patient period to full recovery)) using a time-to-event analysis with a power of 85% at a confidence level of 95%, an accrual period of 730 days and a follow-up period of 180 days, at least 264 patients need to be included in each treatment arm. One percent lost to follow up is estimated so in total 533 patients will be included.

5. TREATMENT OF SUBJECTS

5.1 Investigational product/treatment

Group A: amoxicillin-clavulanate for a total of 10 days. Intravenous administration 4 times a day 1200 mg and switch to oral administration 3 times a day 625 mg after two days and if tolerated. In case of allergy a switch will be made to the combination of ciprofloxacin and metronidazole. In case of intravenous administration ciprofloxacin 2 times a day 400 mg and metronidazole 3 times a day 500 mg. In case of oral administration ciprofloxacin 2 times a day 500 mg and metronidazole 3 times a day 500 mg.

Group B: supportive care and observation only, no antibiotics. Only admittance to the hospital if discharge criteria are not met. (See paragraph 7.3)

5.2 Use of co-intervention

Both treatment arms will be allowed oral intake as tolerated and adequate pain relief.

5.3 Escape medication

No use of Non-Steroidal Anti-Inflammatory Drugs (NSAIDS) for pain medication is allowed. NSAID's are positively associated with increased complicated course of diverticular disease. (4) Pain medication will be up to 4 times a day 1000 mg of paracetamol (oral or iv) and if necessary up to 3 times a day of tramadol 50 mg. If needed Pethidine intramuscular can be added. Psyllium is given as medication in case of constipation.

6. INVESTIGATIONAL MEDICINAL PRODUCT

6.1 Name and description of investigational medicinal product

Amoxicilline 1000 mg-clavulanate 200 mg. Vials of sterile powder. For reconstitution as an intravenous injection or infusion. The amoxicillin is present as amoxicillin sodium and the clavulanic acid is present as potassium clavulanate.
Amoxicilline/ clavulanate tablet 500/125 mg, tablets. Each tablet contains Amoxicillin Trihydrate equivalent to 500mg Amoxicillin and Potassium Clavulanate equivalent to 125mg clavulanic acid.

Amoxicilline/ clavulanate is an antibacterial combination consisting of the semisynthetic antibiotic amoxicillin and the β-lactamase inhibitor, clavulanate potassium (the potassium salt of clavulanic acid). Amoxicillin is an analogue of ampicillin, derived from the basic penicillin nucleus, 6-aminopenicillanic acid. The amoxicillin molecular formula is $C_{16}H_{19}N_3O_5S•3H_2O$, and the molecular weight is 419.46. Chemically, amoxicillin is (2S,5R,6R)-6-[(R)-(-)-2-Amino-2-(p-hydroxyphenyl)acetamido]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid trihydrate.
Clavulanic acid is produced by the fermentation of Streptomyces clavuligerus. It is a β-lactam structurally related to the penicillin's and possesses the ability to inactivate a wide variety of β-lactamases by blocking the active sites of these enzymes. Clavulanic acid is particularly active against the clinically important plasmid-mediated β-lactamases frequently responsible for transferred drug resistance to penicillins and cephalosporins. The clavulanate potassium molecular formula is $C_8H_8KNO_5$ and the molecular weight is 237.25. Chemically, clavulanate potassium is potassium (Z)-(2R,5R)-3-(2-hydroxyethylidene)-7-oxo-4-oxa-1-azabicyclo[3.2.0]-heptane-2-carboxylate.

Ciprofloxacin intravenous 400 mg/200 ml, suspension for intravenous use. Ciprofloxacin intravenous 400 mg/200 ml contains 443 mg ciprofloxacinehydrochloride corresponding to 400 mg ciprofloxacin per 200 ml (2 mg/ml).
Ciprofloxacin 500 mg, tablets. One tablet contains 583,0 mg ciprofloxacinehydrochloride-monohydraat corresponding with 500 mg ciprofloxacin.

Ciprofloxacin is an antibiotic belonging to the quinolone family effective *in vitro* against a large number of Gram-negative aerobic bacteria as well as against some Gram-positive organisms. Ciprofloxacin is the monohydrochloride monohydrate salt of 1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid. It is a faintly

yellowish to light yellow crystalline substance with a molecular weight of 385.8. Its empirical formula is $C_{17}H_{18}FN_3O_3$•HCl•H_2O. Ciprofloxacin is 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid.Its empirical formula is $C_{17}H_{18}FN_3O_3$ and its molecular weight is 331.4. It is a faintly yellowish to light yellow crystalline substance.

Metronidazol 500 mg/100ml suspension for intravenous use. (5 mg/ml)
Metronidazol 500 mg, tablets.

Metronidazol is a synthetic antiprotozoal and antibacterial agent, 1-(β-hydroxy-ethyl)-2-methyl-5-nitroimidazole.

6.2 Summary of findings from non-clinical studies

See Summary of Product Characteristics (SPC).

6.3 Summary of findings from clinical studies

See Summary of Product Characteristics (SPC).

6.4 Summary of known and potential risks and benefits

See Summary of Product Characteristics (SPC).

6.5 Description and justification of route of administration and dosage

For the choice and duration of antibiotics we will follow the practice guidelines of the American Society of Colon and Rectal Surgeons (10) and of the Dutch Stichting Werkgroep Antibiotica Beleid (SWAB). (20) In both a minimum of 7-14 days of broad-spectrum antibiotics is advised. After a minimal period of two days a switch to oral medication is advocated by the SWAB guidelines. Our choice of broad-spectrum antibiotics will be amoxicillin-clavulanate for 10 days in total. Intravenous administration 4 times a day 1200 mg and switch to oral administration 3 times a day 625 mg after a minimum of two days intravenous use and as tolerated. In case of allergy a switch will be made to the combination of ciprofloxacin and metronidazole. In case of intravenous administration ciprofloxacin 2 times a day 400 mg and metronidazole 3 times a day 500 mg. In case of oral administration 2 times a day 500 mg and 3 times a day 500 mg.

6.6 Dosages, dosage modifications and method of administration

Group A: amoxicillin-clavulanate for 10 days. Intravenous administration 4 times a day 1200 mg and switch to oral administration after 2 days when tolerated 3 times a day 625 mg. In case of allergy diagnosed by the treating physician a switch will be made to the combination of ciprofloxacin and metronidazole. In case of intravenous administration ciprofloxacin 2 times a day 400 mg and metronidazol 3 times a day 500 mg. In case of oral administration ciprofloxacin 2 times a day 500 mg and metronidazole 3 times a day 500 mg.

Group B: Observation supportive care only, no antibiotics.

6.7 Preparation and labelling of Investigational Medicinal Product

Both treatment regimes are standard of care in the Netherlands and investigational products used in this trial have been prescribed for diverticulitis for decades. Commercially available IMP's are used that have a MA in the Netherlands. Labelling will be done according to Dutch national law and existing guidelines in local hospitals. To comply to the CCMO guidelines an extra information sticker is attached to the oral regimen box when treated as an outpatient containing the name and identification number of the trial and the name and contact information of the local researcher.

6.8 Drug accountability

Both treatment regimes are standard of care in the Netherlands and investigational products used in this trial have been used for the treatment of diverticulitis for decades. Therefore no separate preparation of study drugs is performed. When patients are randomised to receive antibiotics, antibiotics are already present and available in stock at the different clinical departments. To comply to Good Clinical Practise rules and regulations a drug accountability form is used to be able to trace bath numbers to individual participants. A special trial recipe is used when patients are admitted and randomised for antibiotics. On the ward a list is present to register specific batch for a specific participant and has to be signed by the treating physician for oral and intravenous medication. When a patient is discharged from the hospitals study medication will be supplied by the clinical pharmacy and drug accountability will be registered. A monitor will

be installed and a monitoring program is drafted in collaboration with the Clinical Research Unit of the Academic Medical Centre. The Monitor will check adherence to GCP guidelines on regular intervals and in particular drug accountability registration and report to the steering committee.

7. METHODS

7.1 Study parameters/endpoints

7.1.1 Main study parameter/endpoint

The primary endpoint is time-to-full-recovery with a follow-up period of 6 months. Recovery is defined by all of the following criteria: discharged from the hospital (out-patient), normal diet (defined by tolerating solid food and more than 1L of fluid orally), temperature < 38.0 ℃, and VAS pain score < 4, with no use of daily pain medication and resuming to pre-illness working activities; as assessed by questionnaires and an out-patient clinic visit.

7.1.2 Secondary study parameters/endpoints

- Direct and indirect medical costs at 6 months follow-up;
- Number of days outside the hospital in a 6 months period;
- Occurrence of complicated diverticulitis defined as abscess, perforation, stricture and/or fistula and need for surgery or non-surgical intervention;
- Predefined side-effects of initial antibiotic treatment (e.g. antibiotic resistance/sensitivity pattern, allergy);
- Morbidity, like urinary tract infection, pneumonia, etc;
- Mortality;
- Readmission rate within 6 months and acute diverticulitis recurrence rates at 12 and 24 months follow-up;
- Changes in health status and valuation over time will be measured using generic and disease specific quality of life questionnaires (Euro-Qol 5D, Short Form 36 (SF-36) and the Gastro-intestinal Quality of Life Index (Giqli)) on admission and after 3, 6, 12 and 24 months.

7.1.3 Other study parameters

Sex, co-morbidity, pre-illness working/social activities, surgical history, temperature on admission, diet intake, daily VAS score, white blood cell count (WBC) and C-reactive protein (CRP) level are recorded.

7.2 Randomisation, blinding and treatment allocation

Computerized block randomization for allocation of treatment group, stratified for centre and for Hinchey 1a and 1b, will take place after all inclusion and exclusion criteria have been verified and informed consent has been obtained through the trial website. A standardized case record form (CRF) will be used. This CRF is partially web-based via a secured Internet module. A minimum of 10% of the CRF data will be verified with source data by an independent audit. Because of the design of the study no blinding can be performed for patients or treating physicians.

7.3 Study procedures

Patients will be randomized to one of the following two treatment strategies: (see flowchart table 3.)

A) Conservative strategy **with** antibiotics:

- Hospital admission;
- Intravenous fluids and at least 48 hours of intravenous antibiotics and; subsequently switch to oral antibiotics if tolerated (otherwise continuation i.v.) to complete a full 10-day treatment duration;
- Adequate pain relief;
- Oral intake as tolerated;
- Daily monitoring.

B) Liberal strategy **without** antibiotics (supportive measures only):

- Admission only if discharge criteria are not met;
- No initial antibiotics;
- Intravenous fluids only for those not tolerating oral liquids;
- Adequate pain relief;
- Oral intake as tolerated;
- Daily monitoring when admitted to the hospital;
- Self-monitoring at home (Patient diary with temperature and VAS score until full recovery).

For acute diagnostic work-up: ultrasound or CT proven diverticulitis. In case of diverticulitis-negative US in clinically suspected patients an intravenous contrast-enhanced CT scan is mandatory for confirmation of diverticulitis or exclusion of other pathology. CT for Hinchey/Ambrosetti classification (which is a CT-based classification system) is needed for all patients, but can be delayed 1 day in those with US diagnosis. Staging diverticultis is defined according the modified Hinchey/Ambrosetti staging, only stages 1a and 1b and "mild" diverticulitis (1a Confined pericolic inflammation, 1b Confined small (smaller than 5cm) pericolic abscess) are included. In the attachments we have added a flow chart, showing systematically the inclusion criteria and the following steps after inclusion. (Table 3.)

Both strategies are equal in treatment with the only difference being the use of antibiotics. The use of antibiotics will lead to admittance due to the premise that at least 48 hours of intravenous antibiotics will be given. Admittance in the non-antibiotic group will only be necessary for diagnosis, CT scan within 24 hours, or the need for intravenous liquids (patients with nausea and vomiting), or if patients are in excessive pain not properly reacting to pain medication in the emergency room.

The following data will be obtained and registered: age at first presentation, sex, co-morbidity, pre-illness working/social activities, surgical history, temperature on admission, the interval between start of symptoms and the administration of antibiotics, duration of the period after inclusion and the actual first administration of antibiotics, diet intake, daily VAS score, white blood cell count (WBC) ,C-reactive protein (CRP) level and estimated Glomerular Filtration Rate (eGFR) since intravenous iodinated contrast as well as renally cleared amoxicillin-clavulanate will be administered. WBC and CRP level will be only repeated when clinically necessary.

In-patients: daily monitoring of body temperature, oral intake, pain medication and VAS pain scores. Outpatients will be given a patient diary to daily document body temperature, VAS pain score, use of pain medication and whether normal daily activities are resumed or not, until full recovery criteria are met. At discharge, written and oral instructions are given.

Changes in health status and evaluation over time will be measured using generic and disease specific quality of life questionnaires (Euro-Qol 5D, Short Form 36 (SF-36 and the Gastro-Intestinal Quality of Life Index (Giqli)) on admission and after 3, 6, 12 and 24 months.

Blood cultures are taken on admittance and when clinically deemed necessary.

All patients will undergo colonoscopy at 6 weeks follow up after discharge.

Faeces cultures are taken on admittance and after 3 months.

All of the above mentioned procedures and tests are not different to current clinical practice for diverticulitis in the Netherlands or worldwide. Participants are not submitted to extra invasive procedures or radiation. The only extra Burdon when participating in the study is the filling out of the quality of life questionnaires, the patient diary when treated as an outpatient and the collection of faeces for a faeces culture at the follow up visit after 3 months.

In both strategies CT is repeated in case of clinical deterioration.

For strategy B it can be decided to start antibiotics in case of well-documented clinical deterioration with:

- Temperature > 39.0℃ and/or;
- Positive blood cultures and/or;
- Clinical suspicion of sepsis.

Criteria for sepsis are set by the American College of Chest Physicians and the Society of Critical Care Medicine. Two or more symptoms are required: body temperature <36.0℃ or >38.0℃, heart rate higher than 100 beats a minute, respiratory rate higher than 20 breaths a minute and white blood cell count $<4x10^9$ or $>12x10^9$ cells/L.

Also another infectious focus (e.g., pneumonia, urinary tract infections) may dictate start of antibiotic treatment, instigated by the treating physician.

Discharge criteria:

- Normal diet (defined by tolerating solid food and more than 1L of fluid orally);
- Temperature < 38.0 ℃;
- VAS (Visual Analogue Score) pain score < 4 (with paracetamol only);
- Approval by patient.

Full-recovery criteria:

- Out-patient (see discharge criteria);
- Resuming pre-illness working activities;
- No use of daily pain medication or back to pre-illness pain medication use.

7.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

7.4.1 Specific criteria for withdrawal

Not applicable.

7.5 Replacement of individual subjects after withdrawal

After withdrawal individual subjects will not be replaced.

7.6 Follow-up of subjects withdrawn from treatment

All subjects randomised will be analysed according to the intention to treat principle and follow up will be completed 24 months post discharge.

7.7 Premature termination of the study

An interim-analysis will be performed on the primary endpoint when 50% of patients have been randomised and discharged. An independent statistician, blinded for the treatment allocation, will perform the interim-analysis. The statistician will report to the independent safety-committee. The safety-committee will have unblinded access to all data and will discuss the results of the interim analysis and advice the steering committee. The steering committee will decide on the continuation of the trial. The Peto approach is used: the trial will be ended using symmetric stopping boundaries at P≤0,001.

8. SAFETY REPORTING

8.1 Section 10 WMO event

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

8.2 Adverse and serious adverse events

Adverse events (AEs) are defined as any undesirable experience occurring to a subject during a clinical trial, whether or not considered related to the investigational drug. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

A serious adverse event (SAE):

- Is any untoward medical occurrence or effect that at any dose results in death;
- Is life threatening (at the time of the event);
- Requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- Results in persistent or significant disability or incapacity;
- Is a congenital anomaly or birth defect;
- Is a new event of the trial likely to affect the safety of the subjects, such as an unexpected outcome of an adverse reaction, lack of efficacy of an IMP used for the treatment of a life threatening disease, major safety finding from a newly completed animal study, etc.

When a SAE occurs, the principal investigator will be notified by e-mail or telephone within 24 hours. Using the CCMO module 'ToetsingOnline', all SAEs will be reported to the CCMO and accredited METC that approved the protocol. The reporting will occur within 15 days after the investigator has first received information on the SAE. For fatal or life-threatening cases a preliminary report will be offered within 7 days followed by a complete report within 8 days.

A predefined list of SAEs (inclusive of fatal cases) will be reported expedited within this time frame, namely the following:
- Disease-related major morbidity needing conservative treatment or readmission:
Hinchey 2 / abscess needing percutaneous drainage, ileus, fistula, wound dehiscence/incisional hernia with obstruction, renal failure, myocardial infarction, pulmonary embolus, cerebrovascular accident, gastric or duodenal bleeding, respiratory failure due to pneumonia, pleural effusion or pulmonary edema, urosepsis;
- Disease-related major morbidity needing surgical intervention during first admission or readmission:
Hinchey 2 / abscess needing surgical drainage, Hinchey 3 or 4 diverticulitis (confirmed during surgery), persistent ileus due to stricture / obstruction, incisional hernia, bowel obstruction or herniation due to intra-abdominal adhesions, burst abdomen, abdominal compartment syndrome, fistula, intra-abdominal bleeding, intra-abdominal hematoma, perforation of visceral organ confirmed at surgery, anastomotic leakage, ischemia or necrosis of a visceral organ, enterostomy dysfunction due to prolapse, stenosis or retraction, gastric or duodenal ulcer bleeding needing intervention of any type.

The remaining SAEs are recorded in an overview list (line-listing, instead of individually), that will be submitted periodically (once every half year) to the METC.

8.2.1 Suspected unexpected serious adverse reactions (SUSAR)

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

Unexpected adverse reactions are adverse reactions, of which the nature, or severity, is not consistent with the applicable product information (e.g. Investigator's Brochure for an unapproved IMP or Summary of Product Characteristics (SPC) for an authorised medicinal product).

The sponsor will report expedited the following SUSARs to the METC (through ´ToetsingOnline´):
- SUSARs that have arisen in the clinical trial that was assessed by the METC;
- SUSARs that have arisen in other clinical trial 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 sponsor will report expedited all SUSARs to the competent authority, the Medicine Evaluation Board and the competent authorities in other Member States.

The expedited reporting will occur not later than 15 days after the sponsor 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.

There is no need to break any code in case of a SUSAR because due to the nature of the study in which neither participant nor treating physician are blinded.

8.2.2 Annual safety report

In addition to the expedited reporting of SAEs and SUSARs, the sponsor will submit, once a year throughout the clinical trial, a safety report to the accredited METC, competent authority, Medicine Evaluation Board 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.

8.3 Follow-up of adverse events

All adverse events will be followed until they have abated, or until 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.

8.4 Data Safety Monitoring Board (DSMB)

An independent data and safety monitoring committee will evaluate the progress of the trial and will examine safety parameters at regular intervals (every 25 patients). The committee can unblind the data whenever deemed necessary based on reported adverse events. All involved physicians will repetitively be asked to report any potential adverse events caused by the study protocol. These adverse events will be listed and discussed with the monitoring committee. The monitoring committee can ask for a full report in order to discuss a specific adverse event. A copy of this report will be send to the central ethics board and to the involved physicians. All deceased patients will be evaluated by the safety committee for cause of death and possible trial related serious adverse effects. Every death will be reported to the central ethics board and the local ethics board.
The DSMB will consist of an epidemiologist/statistician who is the chairman, an independent surgeon and an independent radiologist or internist.

8.5 Procedural monitoring by the clinical research unit

AMC´s clinical research unit visits all trial locations up to a total of 4 times; namely after inclusion of the first, 15th and 30th patient, and after full recovery of the last patient. At the different trial sites the practical implementation will be thoroughly examined by means of interviews, evaluation of source documents, assessment of the Trial Master File and Investigator File with evaluation of the administration of essential documents, assessment of patient information, verification of all trial subjects' informed consent forms, studying whether the medical history of the trial subject is in accordance with the in- and exclusion criteria with verification of the exclusion criteria related to the trial subjects' safety for the first 3 trial subjects and at random in 25% of trial subjects, source data verification for the first 3 trial subjects and after that 25% at random, verification of the reporting of SAEs and SUSARs, verification of the administration of the accountability of the investigational medical products and studying whether and how the trial related procedures are described. The clinical research unit writes a monitoring report.

9. STATISTICAL ANALYSIS

The primary endpoint is time-to-full-recovery. Kaplan-Meier curves depicting the proportion of patients with full recovery since randomisation will be constructed for both strategies. The log rank test will be used to test for superiority of one strategy compared with the other. Testing for non-inferiority will be done by calculating the hazard ratio for the liberal strategy compared with the conservative surgery using Cox regression. We will calculate a one-sided 95% confidence interval for this ratio to determine whether it reaches outside the hazard ratio belonging to an equivalence limit of a difference of 5 days in median survival time.

For other end points data will be compared by the Student's t test, Wilcoxon rank sum test, X2 test or Fischer exact test as appropriate.
In superiority tests a two-tailed P value ≤ 0,05 will be considered statistically, whereas one-sided tests will be performed in non-inferiority testing. The main analyses will be based on intention to treat basis.
Predefined subgroup analyses to investigate whether treatment effects are different in subgroups will be performed for Hinchey classification 1a versus 1b.

Cost analysis

All related costs will be estimated based on the actual input terms of resource use and personnel in the 6 months follow-up period after randomization. For all cost-items such as hospital admission, medication used, diagnostic tests, unit costs will be derived from the Dutch costing manual or determined in cooperation with the hospital administration. Direct medical costs will be recorded in the case record forms. Indirect costs arising from losses in productivity will be assessed by means of the Health and Labor questionnaire and will be calculated by means of the friction cost method.

Economic evaluation

The economic evaluation will be performed from a societal perspective as a cost-effectiveness and cost-utility analysis. The main analyses include costs per day reduction to achieve full recovery and costs per QALY gained. Additional sensitivity analyses, regarding differences in possible sub-groups, will be performed.

10. ETHICAL CONSIDERATION

10.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (sixth revision, October 2008) and in accordance with the Medical Research Involving Human Subjects Act (WMO) and other guidelines, regulations and Acts such as Good Clinical Practice.

10.2 Recruitment and consent

Patients will be recruited by treating physicians at the different hospitals. The treating physician will inform patients and written informed consent is obtained. Participants will be given as much time as they desire to consider their decision

10.3 Objection by minors or incapacitated subjects

Not applicable.

10.4 Benefits and risks assessment, group relatedness

In all international treatment guidelines antibiotic therapy is always advised. Anaerobes are the most commonly isolated organisms in acute diverticulitis. Gram-negative aerobes and facultative gram-positive bacteria are often cultured as well. Therefore, broad-spectrum antibiotics are advised. Patients should start with intravenous antibiotics and after improvement within 2-4 days oral antibiotics are continued to a complete 7-10 day treatment. In the Netherlands antibiotics are **not** considered primarily indicated as stated in the SWAB (Stichting Werkgroep Antibiotica Beleid) guidelines (20) (table 2). A recent survey held among surgeons and gastroenterologists in the Netherlands indicate that 90% of both surgeons and gastroenterologists do not routinely use antibiotics in the treatment of acute uncomplicated diverticulitis. (19) Adverse effects of the use of antibiotics are well known, such as allergic reactions, development of antibiotic resistance of bacterial species, and various side effects. The frequency of toxicodermia is 7-8% with amoxicillin, allergic reactions are accounted for 1% of the patients and the incidence of anaphylactic shock is between 0.01-0.04% with the use of penicillin. With the use of other antibiotics allergic reactions are less but there is a much higher incidence of nephro-

toxicity. Over the last decade there have been efforts made to minimize the prescription of antibiotics in various fields in clinical medicine. Examples are appendiceal mass, acute cholecystitis, and this is also true for community-acquired infections, such as acute otitis media, upper respiratory tract infections and in paediatric medicine. Resistance to antibiotics is a major public-health problem and antibiotic use is being increasingly recognized as the main selective pressure driving this resistance.
The potential benefits of a more liberal treatment strategy for acute diverticulitis include shorter duration of hospital admission, cost reduction, less antibiotic resistance development and side effects. The potential harms of the liberal strategy include higher readmission rates, delayed treatment of infectious complications, higher treatment failure rate, more complicated disease and extra costs related to additional procedures. The actual balance between clinical effects and costs for both strategies is not known. Uncomplicated diverticulitis usually is a self-limiting disease and accounts for almost 90% of the patients with diverticulitis. Our study design reflects current clinical practice in which two different approaches are commonly applied next to each other; with or without the use of antibiotics.

10.5 Compensation for injury

The sponsor/investigator has a liability insurance, which is in accordance with article 7, subsection 6 of the WMO.

The sponsor (also) has an insurance, which 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 23rd June 2003). This insurance provides cover for damage to research subjects through injury or death caused by the study.

1. € 450.000,-- (i.e. four hundred and fifty thousand Euro) for death or injury for each subject who participates in the Research;
2. € 3.500.000,-- (i.e. three million five hundred thousand Euro) for death or injury for all subjects who participate in the Research;
3. € 5.000.000,-- (i.e. five million Euro) for the total damage incurred by the organisation 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.

10.6 Incentives

No incentives are used.

11. ADMINISTRATIVE ASPECTS AND PUBLICATION

11.1 Handling and storage of data and documents

Blinded investigators not involved in patient care will perform collection and evaluation of all data. All primary endpoints will be crosschecked with data from primary sources (by an independent data manager blinded for treatment allocation). An independent adjudication committee will perform a blinded outcome assessment of the primary endpoint. Data will be handled confidentially and anonymously. A subject identification code is used to link the data to the subject. A unique code is generated for each individual and is not based on the patient initials and birth-date. The principal investigator safeguards the key to the code. The handling of personal will comply with the Dutch Personal Data Protection Act (in Dutch: De Wet Bescherming Persoonsgegevens, WBP). The project leader will keep the source data for 15 years.

11.2 Amendments

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.

11.3 Annual progress report

The sponsor/investigator 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, numbers of subjects included and numbers of subjects that have completed

the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

11.4 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.

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.

11.5 Public disclosure and publication policy

The study protocol will be offered to BMC Surgery for publication. Pubmed has a free full-access link to BMC Surgery. Presentations of both the study protocol and the study results will be held at the conferences of the Dutch Society of Gastroenterology (NVGE vergadering) and the Dutch Society of Surgeons (Chirurgendagen).
After completion of the study and analysis of the data results will be made publically without restriction, independent of the outcome. They will be submitted for publication to an international peer-reviewed journal.

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13. Table 1. Hinchey classification and modified Hinchey classification of acute diverticulitis

Hinchey	Modified Hinchey
	0 Mild clinical diverticulitis
I Pericolic abscess or phlegmon	**Ia** Confined pericolic inflammation
	Ib Confined small pericolic abscess
II Pelvic, distant intra-abdominal, or retroperitoneal abscess	**II** Pelvic, distant intra-abdominal, or retroperitoneal abscess
III Generalized purulent peritonitis	**III** Generalized purulent peritonitis
IV Generalized fecal peritonitis	**IV** Generalized fecal peritonitis

14. Table 2. Treatment guidelines in the United States en the Netherlands

American Society of Colon and Rectal Surgeon.	SWAB (Stichting Werkgroep Antibiotica Beleid)
Always antibiotics	*Antibiotics primarily not indicated*
Out-patients: Metronidazole 500mg 3 times a day + Ciprofloxacin 500–750 mg 2 times a day or Amoxicillin–clavulanate 625 mg 3 times a day	Amoxicilline-clavulanate 1000/200 mg 4 dd iv; 7-14dg or Cefuroxim and metronidazole 500 mg 3 dd iv; 7-14 dg + or Amoxicilline 1000 mg 4 tot 6 dd iv; 7-14dg + Aminoglycoside 1 dd iv + Metronidazole 500 mg 3 dd iv; 7-14dg
Intravenous regimens for in-patients Metronidazole 500 mg 3 times a day + Ciprofloxacin 400 mg 2 times a day or Metronidazole 500 mg 3 times a day + Third-generation cephalosporin (e.g., ceftriaxone — 1–2 g every 24 hr)	

15. Table 3. Flowchart DIABOLO trial