**DIRECT trial**

*Diverticulitis Recurrences or Continuing symptoms:*

*Operative versus Conservative Treatment*

*A MULTICENTER RANDOMISED CLINICAL TRIAL*

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### PROTOCOL TITLE
*Treatment of Diverticulitis Recurrences: Operative versus Conservative*

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SUMMARY

Rationale: Persisting abdominal complaints are common after an episode of diverticulitis treated conservatively. Furthermore, some patients develop frequent recurrences. These two groups of patients suffer greatly from their disease impairing quality of life and increasing costs due to multiple specialist consultations, pain medication and sick-leave from paid work.

Both conservative and operative management of patients with persisting abdominal complaints after an episode of diverticulitis and/or frequently recurring diverticulitis are applied. However, direct comparison by a randomised controlled trial is necessary to determine which is superior in relieving symptoms, optimalising QoL, minimising costs and preventing diverticulitis recurrences against acceptable morbidity and mortality associated with surgery or the occurrence of a complicated recurrence after conservative management.

We, therefore, constructed a randomised clinical trial comparing these two treatment strategies.

Objective: The objective is to compare the outcome of elective resection of the diseased colon segment to conservative management for patients with persisting abdominal complaints after an episode of diverticulitis and/or frequently recurring diverticulitis.

Study design: Multicenter randomised clinical trial with a follow-up of 1 year.

Study population: Patients (18-75 years) presenting themselves with persisting abdominal complaints after an episode of diverticulitis and/or three or more recurrences within 2 years.

Intervention (if applicable): Patients randomised for conservative treatment are treated according to the current daily practice (antibiotics, analgetics and/or expectant management). Patients randomised for elective resection will undergo an elective resection of the affected colon segment. Preferably, a laparoscopic approach is used.

Main study parameters/endpoints: Quality of life measured by the Gastro-intestinal Quality of Life Index, Shortform-36, EuroQol-5D and visual analogue scale for pain quantification. Secondary endpoints are morbidity, mortality and total costs.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: The filling out of the quality of life questionnaires and abdominal complaint assessment at inclusion will take approximately 40 minutes of the patient’s time. Also, patients may be confronted with the possible, but unlikely, unfavorable outcome of elective resection.

The potential benefits of participation in this study for this specific group of patients is a potential final answer to the much debated discussion about the optimal treatment persisting abdominal complaints after an episode of diverticulitis and/or frequently recurring diverticulitis. The close follow-up regarding objective and subjective outcome of treatment in the studied subjects is also likely to be beneficial.
1. INTRODUCTION AND RATIONALE

1.1 Diverticulosis

Diverticular disease of the colon is a common disease in the modern western world and includes diverticulosis and diverticulitis. Diverticula are outpouchings that occur at weak points in the colonic wall where small blood vessels enter the circular muscle layer. Diverticulosis is most frequently found in the distal part of the colon, with 90% of patients having the sigmoid colon involved. Rarely do patients have disease isolated to other colonic locations without evidence of diverticulosis in the sigmoid colon.

The pathophysiology of diverticulosis is likely to be related to the combined action of age, dietary factors, colon structure and motility;¹ Low-fibre diet increases the transit time which is associated with increased dessication and viscosity of the faecal content.² As an adaptive mechanism, intra-colic pressure increases. In short, such a low-fiber diet results in a small stool which requires high intracolic pressure for propulsion. Additionally, structural changes take place with advancing age that reduce the tensile strength and elasticity of the colonic wall.³ All these factors contribute to the development of diverticulosis.

The incidence of diverticulosis increases with age, varying from less than 10% in patients younger than 40 years of age to an estimated 50-70% of patients above 80 years.⁴-⁵

1.2 Complicated diverticulosis: Diverticulitis

Most patients who have diverticulosis remain asymptomatic; however an estimated 15-20% will develop diverticulitis.⁶ Acute diverticulitis is a complication of diverticulosis that occurs when these outpouchings become infected. The pathogenesis of diverticulitis is uncertain. However, stasis of or obstruction by fecal matter in the narrow entrance of the diverticulum may lead to bacterial overgrowth.
and local tissue ischemia, ultimately leading to perforation.

1.3 Epidemiology

In the Netherlands, an increase in hospital admissions for diverticular disease has been seen over the last few years. In 2002 diverticular disease led to approximately 90,000 hospital admissions and reached 135,000 admissions in 2006, with a distinct female predominance (60%). Data on the incidence of diverticulitis in the Netherlands is lacking, but has been estimated at around 75 to 150 in 100,000 individuals per year. In the United States of America, the annual incidence of diverticulitis is estimated at around 10 in 100,000 individuals and leads to 200,000 hospital admissions per year. 3,7-8

1.4 Clinical presentation

Diverticulitis can range form mild to severe. Mild cases of diverticulitis are uncomplicated and present with mild symptoms (abdominal pain, fever, diarrhea) or confined pericolonic inflammation. Physical examination may reveal tenderness in the right or left iliac fossae and occasionally the presence of a palpable tender mass. Initial bloodtests typically show elevated inflammatory markers.

Severe, complicated cases with perforation may be associated with intra-abdominal abscess, generalized, purulent peritonitis, fistula formation, bleeding or obstruction. The extent of the perforation determines the clinical behavior. Microperforations remain localised because they are contained by pericolic fat and mesentery, leading to the formation of small pericolic abscesses. Larger macroperforations may result in more extensive abscesses, even extending to other organs causing fistulous disease. Left untreated, fibrosis and strictures
may be formed. Free perforation into the peritoneum causing purulent or feculent peritonitis can be life threatening, but are very uncommon.

1.5 Diagnosis

An efficient radiologic approach in the diagnosis of acute diverticulitis is ultrasound (US); it is low-cost and non-invasive. In experienced hands, US has an overall sensitivity of 77% and specificity of 99%. In cases of uncomplicated diverticulitis it has a sensitivity of 96%.\(^9\) The optimal, but more expensive, option is the use of Computed Tomography (CT) for the diagnosis of diverticulitis. It has a sensitivity ranging from 85% to 97%.\(^{10-11}\) In addition to establishing the diagnosis of acute diverticulitis, it can help identify colonic perforation, abscess formation, colonic strictures and fistula formation, which can have a direct impact on the management of the patient. Recent preliminary data suggests that CT is significantly superior to US in the detection of urgent diseases, such as acute diverticulitis, in an unselected patient population presenting themselves with acute abdominal pain at the emergency department.\(^{12}\) Thus, CT has become the most suitable primary imaging approach for the diagnosis of acute diverticulitis.

1.6 Classification

Ambrossetti et al. classified acute diverticulitis as mild or severe according to the finding at CT. Mild diverticulitis was described as bowel wall thickening (<5mm) and pericolic fat stranding. Severe diverticulitis was defined as bowel wall thickening greater than 5 mm, localised perforation or subdiaphragmatic air and abscess (appendix 12.2).\(^{13}\) Hinchey developed another classification, based on CT findings, to distinguish the four stages of acute complicated diverticulitis (appendix 12.1).\(^{14}\) Advancements in imaging modalities
have led to several modifications to the Hinchey classification. New subcategories have been added that take radiological findings into consideration. The Modified Hinchey classification is now mostly used to distinguish the four stages (appendix 12.1).

1.7 Treatment of acute diverticulitis (first episode)

At present, the management of a first episode of acute diverticulitis is largely based on the stage of the disease at the time of presentation and by the response to the initial treatment. Many clinicians treat mild diverticulitis conservatively either with or without antibiotics and a low-residue liquid diet unless there is an absolute indication for surgery (eg. peritonitis) as they claim that 50% to 80% of patients with a first episode of acute diverticulitis respond to this conservative approach and do not require surgery.

When perforation of a diverticulum occurs, an intra-abdominal abscess may be formed. Many patients who have small (4 cm or less) pericolic abscesses without peritonitis (Hinchey stage Ib) can be treated conservatively with restricted oral intake and broad-spectrum antibiotics. For patients with larger (4 cm or larger) peridiverticular abscesses (Hinchey stage II) CT-guided percutaneous drainage may well be beneficial. Percutaneous drainage has the advantage that it can control sepsis immediately. It may also allow for elective rather than emergency surgery, reducing the likelihood of a two-stage procedure.

The treatment options mentioned above are however based on retrospective studies. No definitive answer has been found to the question to what the optimal treatment is for a first episode of diverticulitis. On the other hand, there is generally little doubt about patients, who do not respond to conservative treatment or suffer from a generalized peritonitis (Hinchey stage III or IV), being surgically treated.
1.8 Persisting abdominal complaints after an episode of diverticulitis

The recurrence rate of patients treated conservatively for an episode of diverticulitis is approximately 25%. Elective resection has traditionally been advised after a second episode of diverticulitis. It has been thought that patients a diverticulitis recurrence are at greater risk of developing complications, have higher mortality rates and are less likely to respond to medical treatment. However, recent studies have demonstrated that the number of attacks of diverticulitis is not necessarily a prevailing factor in defining the suitability of surgery. Most patients who present with complicated diverticulitis do so at the time of their first attack. Furthermore, only a fraction (5-7%) develops complicated diverticulitis during subsequent attacks. This and the fact that operation itself carries significant morbidity and mortality, has lead to reluctance in gastroenterologists and surgeons towards elective resection after a recurrence of the disease.

However, elective resection may be an appropriate solution for a more selective group of patients who suffer greatly from their disease. Many studies have consistently shown that 40-80% remain symptomatic after conservative treatment leading to impaired quality of life (Qol) and increased costs due to multiple specialist consultations, pain medication and sick-leave from paid work. Logically, this is also the case for patients who continue developing diverticulitis recurrences on a frequent basis. Also, these patients often remain symptomatic in between the recurrences.

In addition of possibly preventing further recurrences and complications of diverticulitis, elective resection has frequently been demonstrated to relieve persisting symptoms after an episode of diverticulitis. Therefore, many physicians and patients seem to abandon expectant/conservative management and subsequently choose elective resection.
Both conservative and operative management of patients with persisting abdominal complaints after an episode of diverticulitis and/or frequently recurring diverticulitis persisting are applied. However, direct comparison by a randomised controlled trial is necessary to determine which is superior in relieving symptoms, optimalising QoL, minimising costs and preventing diverticulitis recurrences against acceptable morbidity and mortality associated with surgery or the occurrence of a complicated recurrence after conservative management.

2. OBJECTIVES

Primary Objective
To compare the outcome of elective surgery to conservative treatment for patients with persisting abdominal complaints after an episode of diverticulitis and/or frequently recurring diverticulitis.

3. STUDY DESIGN

Randomised clinical multicenter trial with a follow-up of 1 year for all patients. This will be performed in a clinical and out-hospital setting.

4. STUDY POPULATION

4.1 Population (base)
Study subjects are selected from a clinical population in the Netherlands of the Meander Medical Center (Amersfoort), Onze Lieve Vrouwe Gasthuis (Amsterdam), Reinier de Graaf Gasthuis (Delft), Sint Antonius Ziekenhuis (Nieuwegein), Diakonessenziekenhuis (Utrecht),
Rode kruis ziekenhuis. Kennemer Gasthuis, Laurentius ziekenhuis, Atrium Medisch Centrum, Sint Lucas Andreas ziekenhuis, Jeroen Bosch ziekenhuis, Maasstad ziekenhuis, Maxima Medisch Centrum, Medisch Spectrum, IJsselmeerziekenhuis and Groene Hart ziekenhuis on a consecutive basis.

4.2 Inclusion criteria

- Age 18-75 years.
- Patients presenting with either persisting abdominal complaints and/or frequently recurring diverticulitis after a well documented (CT-scan, sonography or endoscopy) episode of diverticulitis.

Persisting abdominal complaints may include patients with:

- continuing lower left abdominal pain AND/OR persistent change in bowel habits AND/OR persistent blood loss.
- Symptoms must exist longer than 3 months after a previous episode of diverticulitis
- Symptoms must be accompanied by changes in the colonic wall on a recent CT-scan, sonography or endoscopy.

Frequently recurring diverticulitis is defined as:

- A total of three or more in-hospital presentations for an episode of diverticulitis within 2 years. As described previously, (at least) one episode must be well documented (CT-scan, sonography or endoscopy).
- A minimal interval of 3 months between the episodes is mandatory.
- Patients with American Society of Anaesthesiologists classification of preoperative risk I,II or III.
4.3 Exclusion criteria

- Patients with elective or emergency surgery for acute diverticulitis in the past.
- Patients with an absolute operation indication (perforation with purulent/fecal peritonitis, symptomatic bowel stenosis or fistula).
- Patients with colorectal malignancies.
- Patients with a psychiatric disease or other conditions making them incapable of filling out the questionnaires or completing the objective follow up tests.
- Patients in ASA class III who are at high risk for per- and postoperative complications due to severe co-morbidity as regarded by the surgeon and/or the patients specialists.

4.4 Endpoints, hypothesis and sample size calculation

The comparison between elective surgery and conservative treatment is the basic principal of the following endpoints/hypothesis.

Primary endpoint

Quality of life (QoL) objectified primarily by the Gastro-intestinal Quality of life Index (GIQLI) after a follow-up of six months.

The results of the primary analysis will be reported and published after six months follow-up of all patients.

Secondary endpoints

1. QoL objectivied secondarily by the GIQLI, EuroQol-5D (EQ-5D), Short-form 36 (SF-36), Visual Analogue Score (VAS) for pain and a ROME III questionnaire after a follow-up of three years.
2. Mortality defined as:
   - **Elective surgery**: 30-days mortality.
   - **Both groups**: Mortality associated with the development of a complicated recurrence of diverticulitis during follow-up.

3. Morbidity defined as:
   - Diverticulitis recurrence*
   - Perforation (with purulent/fecal peritonitis)
   - Fistula
   - Symptomatic stenosis
   - Abcess
   - Stoma formation
   - Emergency surgery or re-operation
   - Peri- and postoperative complications

4. Direct health care costs. In-hospital resource use will be recorded. During follow-up medication use, general practitioner and specialist visits will be measured at regular intervals with customized questionnaires.

5. Indirect non-health care costs, using a standardised ShortForm-health and labour questionnaire.

6. Correlation between the GIQLI score and a 7-point scale reflecting self-reported improvement.

The investigations undertaken to quantify these endpoints are described in section 6.1.1 and 6.1.2.
4.4.1 Hypothesis primary endpoints

Quality of life will better in the elective surgery group compared to conservative treatment.

4.4.2 Hypothesis secondary endpoints

Ad 1. Mortality will be nihil in both groups.
Ad 2. Morbidity will be similar in both groups
Ad 3 Direct health care costs are expected to be equal or slightly lower for conservative treatment compared to elective resection.
Ad 6. Indirect non-health care costs are higher for conservative treatment compared to elective resection.

4.4.3 Sample size calculation

The sample size calculation will be based on the primary endpoint. Forgione et al and Zdichavsk et al demonstrated an improvement of 10 points on the Gastro-Intestinal Quality of Life Index (GIQLI) in patients before (100 ± 22.1 and 95.3 ± 21.4) and one month to one year after elective resection (111 ± 20.4 and 105.8 ± 15.5) for diverticulitis. The correlation coefficient was 0.3. Based on these results, using an independent t-test (alpha=0.05, delta=10, sigma = 21, power =0.9) approximately N=97 patients per group are needed for this study. This amount changes minimally when ANCOVA (correlation coefficient 0.3) is used (N=86 patients). Therefore a total study population of 194 patients is required to attain statistical significance. To compensate for a potential loss to follow-up of 10%, 214 patients will be included. Follow-up will be conducted on the intention-to-treat principle.
5. TREATMENT OF SUBJECTS

5.1 Investigational treatment

5.1.1 Conservative treatment

Patients randomised for conservative treatment are treated according to the current daily practice. In other words, conservative treatment is determined by the preferences of the treating physician. Conservative treatment may consist of expectant management, antibiotics and/or analgetics. Should there be radiologic evidence for the presence of pericolic abscesses, percutaneous drainage may be performed depending on the size and opinion of the local radiologist regarding accessibility.

5.1.2 Elective surgery

Patients randomised for elective surgery will undergo an elective colonic resection within approximately 2 months of follow-up. In the interval between randomisation and elective surgery, patients are treated conservatively (see above). Intentionally, a laparoscopic approach is used. The extent to which the colon is resected in the proximal direction should cover the entire macroscopically involved colon. In other words, the proximal resection line should be where no diverticula exist or at the level where a considerable decline in number of diverticula is noted. Distally, the margin of resection should be where the taenia coli splay out onto the upper rectum. After resection a primary anastomosis will be performed between the distal colon and rectum.

5.2 Use of co-intervention

At hospital discharge patients are advised to use a high-fiber diet during the follow-up period. Patients are allowed to use any kind of co-medication.
5.3 Escape medication

The treating physician may use any analgetic necessary to treat pain complaints of the patients. There are no limitations in escape medication.

6. METHODS

6.1 Study parameters

6.1.1 Primary and secondary endpoints:

To investigate and quantify the primary and secondary endpoints we will undertake the following investigations (appendix 12.3).

Measurements at baseline

- Quality of life: Patients are asked to fill out the Gastro-intestinal Quality of Life Index (GIQLI), EuroQol-5D (EQ-5D), Short Form 36 health survey (SF-36), the ROME III questionnaire and a visual analogue scale for pain quantification (VAS) at baseline (appendix 12.4.1).

- (In)direct (non)-healthcare costs: Patients are asked to fill out the Short Form Health and Labour (appendix 12.4.3) and the customised health care consumption questionnaire (appendix 12.4.4).

- Baseline characteristics: Data regarding patient characteristics, current complaints, comorbidities, medical history (appendix 12.4.5) will be collected.

Measurements during follow-up

- Quality of Life: The Gastro-intestinal Quality of Life Index (GIQLI), EuroQol-5D (EQ-5D), VAS, ROME III questionnaire and Short Form 36 health survey (SF-36) will be used to evaluate the
effect of conservative treatment or surgery on the quality of life (appendix 12.4.2).

Furthermore, patients are asked point out on a 7 point scale whether their health/complaints have improved or deteriorated. All questionnaires are asked to be filled in at 3, 6, 9, and 12 months after conservative treatment or elective surgery. In addition, when patients in the conservative group undergo/switch to elective resection due to severe abdominal symptoms (see randomisation, blinding, treatment allocation and event assessment), they are also asked to fill in these questionnaires.

- Morbidity and mortality: At inclusion, patients will be instructed to return to the local hospital should an event occur which requires hospitalisation. In addition, patients are asked for any events leading to hospitalisation or specialist/general practitioner consultation at regular intervals (3, 6, 9, and 12 months) (appendix 12.4.4). Should an event have occurred, data regarding that event will be collected (appendix 12.4.7).

Data regarding peri- and postoperative complications after elective resection will also be collected (appendix 12.4.6).

- Direct health care costs: These costs include costs related to hospitalisation, imaging, blood tests, colonoscopy, medication, interventions, operations, consultations, complications and primary health care contacts. On an individual patient basis, resource use will be recorded. Subsequently, by multiplying resource use with unit price and reckoning with the number of recurrences, actual in-hospital costs per patient will be calculated. Unit costs will be derived from the Dutch costing manual or determined in co-operation with hospital administration. Health care consumption including general practitioner or specialist visits and medication use will be assessed using customised questionnaires and case report forms (appendix 12.4.4). These will we sent to the patients at 3, 6, 9, and 12 months after treatment.
- **Indirect health care costs:** These costs include sick leave from paid work. This will be assessed using the ShortForm- Health and Labour questionnaire (appendix 12.4.3). This questionnaire is sent to the patients at 3, 6, 9, and 12 months after treatment.

### 6.2 Randomisation, blinding, treatment allocation and event assessment

All patients presenting themselves with persisting abdominal complaints after an episode of diverticulitis and/or a third (or more) diverticulitis recurrence, require to have had a recent radiological examination of the abdomen. (appendix 12.3). Preferably a CT-scan is used. However, sonography may also be used on the condition that bowel wall thickening (millimetres) and abscess size can be assessed accurately. Colonoscopy may be performed on indication to exclude malignancy.

If all inclusion criteria are met, patients are informed about the study protocol by their treating physician or the local coordinator. They are given a 3 day reflective period, together with the information package (appendix 12.5). After the reflective period, the patient is contacted and asked for participation. If the patient decides to take part in the trial, he/she is invited to the local hospital to sign the informed consent (appendix 12.6). After receiving this consent form, data regarding baseline characteristics will be collected, randomisation will be performed, questionnaires will be asked to be filled out and scheduled to be sent. Furthermore logistics for the (potential) elective resection will be arranged.

Both patients in the conservative and elective resection group will be treated conservatively in case of events during follow-up unless there is an absolute indication for surgery according to the treating physician (e.g. fistula, symptomatic stenosis, perforation with purulent/fecal peritonitis). In addition, in case of persisting abdominal symptoms during follow-up (in the conservative group) which are regarded as unbearable by both patient and
treating physician, the treating physician may consult an independent event adjudication committee. The independent committee will advice the treating physician whether or not to abandon conservative management and proceed to elective resection.

6.3 Study procedures

Sonography or CT-scan

These examinations are usually performed in patients with persisting abdominal complaints after an episode of diverticulitis. Thus, they are reckoned among the standard medical follow-up.

Assessment of baseline characteristics.

If the patient decides to participate in the trial, he/she will be invited to the local hospital for assessment of the baseline characteristics. Patients will be asked questions regarding their medical history and health status (appendix 12.4.5). Also data regarding radiological examinations will be collected.

Quality of life questionnaires

Validated QoL questionnaires will be used (appendix 12.4).

- Gastro-intestinal Quality of Life Index (GIQLI): a questionnaire containing 36 questions on gastro-intestinal complaints.

- EuroQol-5D: a questionnaire containing 5 questions on different dimensions of well-being.
- Short Form (SF)-36: a questionnaire containing 36 items regarding general quality of life.

- Visual analogue scale (VAS): A scale for pain quantification.

- 7 point scale for health/complaint status: The 7 point scale will be used as an “anchor” for the GIQLI score. This creates the possibility to examine the correlation between the GIQLI score and the 7 point scale reflecting self-reported improvement.

- The ROME III questionnaire: A table containing questions on gastro-intestinal symptoms. Patients are asked to indicate the extent of their symptoms.

**Direct and indirect health care costs questionnaires**

A validated health and labour questionnaire will be used to asses sick leave from paid work and a customised questionnaire for health care consumption.

- Short Form Health and labour: a questionnaire containing 14 items regarding sick leave from paid work.

- Customised health care consumption questionnaire: a questionnaire containing 15 items on health care consumption.

**Event assessment questionnaire**

A questionnaire on events leading to hospitalisations and/or specialist/general practitioner consultation will be used to asses diverticulitis recurrences (and complications), morbidity and mortality. This questionnaire is incorporated in the customised health care consumption questionnaire.

Furthermore patients will be instructed to return to the local hospital should an event occur which requires hospitalisation.
6.4 **Withdrawal of individual subjects**

Subjects can leave the study at any time for any reason if they wish to do so without any consequences.

6.5 **Replacement of individuel subjects**

Inclusion will proceed until at least 107 patients are included in each group. Reasons for withdrawal will be recorded accurately. This study is conducted according the intention to treat principle.

6.6 **Follow-up of subjects withdrawn from treatment**

Patients withdrawn from the study will receive the regular out-patient follow up.

6.7 **Premature termination of the study**

An independent Data and Safety Monitoring Board (DSMB) will be established to monitor the progress of the study and ensure that the safety of subjects enrolled in the study is not compromised. The DSMB will consist of physicians and a statistician experienced in clinical studies and will be supported by an unblinded trial statistician at an independent research group. Details of the composition, roles, responsibilities, and processes of the DSMB are documented in the DSMB charter. The independent DSMB will review safety data may recommend that the study be stopped or amended based on safety findings.

No single statistical decision rule or procedure can take the place of well-reasoned consideration of all aspects of the data by a group of concerned, competent and experienced persons. However, the DSMB will consider the following criteria, taking into account the
sample size at the time of analysis, in determining whether to recommend premature termination.

Safety:

All mortality cases and other (serious) adverse events as listed in section 7.2 will be reported to the METC and to the DSMB. Safety data will be examined after 25%, 50% and 75% inclusion. Treatment-related in-hospital mortality greater than 5% for patients in the elective surgery group is cause for alarm.

Recurrence of diverticulitis is an important, though secondary, endpoint. A difference in recurrence rate of >40% between the conservative group and elective surgery group is of concern.

Efficacy:

A formal interim analysis of the efficacy data, after 33% of the target sample size has completed six months of follow-up, will be performed according to the procedure described in section 8.4. A difference of 10 points on the GIQLI score is considered clinically relevant.

Procedure in case of termination

If, after interim analysis (chapter 9.4), one of the abovementioned criteria is met the study will be terminated and the following steps will be taken:

- Notification of the project leader.
- Notification of the medical ethical technical committee (METC)
- All patients randomised for the study will be notified and will receive the standard follow-up.
7. **SAFETY REPORTING**

7.1 **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.

7.2 **Adverse and serious adverse events**

Complications of laparoscopic colorectal surgery: 53-57

- Anastomotic leak 3.0%
- Wound infection 2.9%
- Pulmonary infection 2.5%
- Urinary infection 7.8%
- Cardiogenic pulmonary edema 0%
- Postoperative ileus 3.2%
- Urethral injury 1.3%
- Conversion 6.6%
- Mortality 1.1%
- Thrombosis 0.3%
- Peri-and postoperative bleeding 1.0%

Complications of conservative treatment:

- Recurrent diverticulitis.
- Perforation caused by a severe diverticulitis recurrence.

All abovementioned adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded. All adverse events will be reported to the accredited METC that approved the protocol, according to the requirements of that METC.
All SAE’s will be reported to an independent safety-committee. The safety-committee will discuss the SAE’s and give advice to the trial steering-committee.

Adverse events which occur frequently after elective resection such as postoperative nausea, pain and fatigue will not be registered unless the treating physician considers these symptoms as unusually severe.

7.3 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. These additional events will also be conducted for general overview and inclusion in the cost-effectiveness analysis.

8. STATISTICAL ANALYSIS

The statistical package SAS will be used for analysis. All analyses will be performed according the intention to treat principle.

Baseline characteristics will be described as means and standard deviations (continuous variables) or counts and percentages (categorical variables).

The primary outcome is the difference in GIQLI between the two treatment groups at six months. The difference between the groups will be analysed using a mixed model with repeated measures for time and will include all data from patients for the first six months post-randomisation. The fixed model will include the variables time (categorical), treatment group, a group*time interaction and the baseline GIQLI; the difference in GIQLI at six
months will be tested using a linear contrast. The variance-covariance matrix will be modelled as unstructured.

Secondary analyses will include an examination of the difference in GIQLI scores between the two groups over the full three year follow-up, and an investigation of differences between the randomisation groups for the secondary endpoints (EQ-5D, SF-36, VAS, ROME III score) over the full course of the study. Mixed models will be used to account for repeated measures per patient. Additionally, the correlation between the GIQLI and the 7 point scale reflecting self-reported improvement of complaints over time will be examined.

8.4 Interim analysis

The independent statistician supporting the DSMB will conduct the following interim safety and efficacy analyses. A more detailed description can be found in the DSMB charter.

Safety:

After inclusion of 25%, 50%, 75% of patients, incidence of all (serious) adverse events listed in section 7.2 will be examined. Occurrence of anastomotic leak, wound infection, pulmonary infection, urinary infection, cardiogenic pulmonary edema, postoperative ileus, urethral injury, conversion, mortality, thrombosis, peri-and postoperative bleeding will tabulated for the elective surgery group. Treatment groups will be compared with respect to the incidence of recurrent diverticulitis and perforation caused by a severe diverticulitis recurrence.

Efficacy:

After 33% of the 214 expected patients have completed six months’ follow-up, one formal interim analysis of the primary efficacy endpoint by randomized treatment arm will be prepared by the trial statistician using the mixed model described in section 8, “Statistical
Analysis”. All patients with at least 3 months of follow-up at the time of interim analysis will be included in the interim analysis. When 33% of the patients have six months of follow-up, 50-65% of the total sample will have been included in the study and nearly half will have at least three months of follow-up.

Following the analysis, the DSMB may recommend stopping the trial for early proof of efficacy. To guarantee an overall significance level of 0.05, the alpha spending approach proposed by Lan and DeMets will be applied to O’Brien-Fleming stopping boundaries in order evaluate of the difference in the GIQLI score between treatment arms. The significance level of the interim analysis will be calculated based on the percentage of follow-up in months (up to and including six months) for all patients included in the interim analysis relative to the planned number of follow-up months (again, up to and including six months) for all patients at the final analysis. Using intention-to-treat analysis, the 10% overrecruitment for loss to follow-up proposed in section 4.4.3 will more than compensate for the negligible loss of power due to O’Brien-Fleming alpha adjustment.

9. ETHICAL CONSIDERATIONS

9.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (version 2008, Seoul) and in accordance with the Medical Research Involving Human Subjects Act (WMO).

9.2 Recruitment and consent

Patients will be recruited from a clinical population affiliated with the Meander Medical Center, Onze Lieve Vrouwe Gasthuis, Reinier de Graaf Gasthuis, Diakonessenhuis and Sint
Antonius Ziekenuis. Patients will be informed about the study by their supervising/coördinating physician and will receive a patient information letter (appendix 12.5). They will be asked for their written consent by the local coordinator (appendix 12.6). They will be given three days to consider their decision.

9.3 Benefits and risks assessment, group relatedness

The selected group consists of patients with persisting abdominal complaints after an episode of diverticulitis.

Benefits

The potential benefits of participation in this study for this specific group of patients is a potential final answer to the much debated discussion about the optimal treatment for persisting abdominal complaints after an episode of diverticulitis and/or three or more recurrences within 2 years.

The close follow-up regarding objective and subjective outcome of treatment in the studied subjects is also likely to be beneficial.

Burdens

- The filling out of the quality of life questionnaires. The filling out of these surveys will take approximately 30 minutes of the patient’s time.
- Patients are asked to visit the local hospital for signing the informed consent and collecting baseline data. Collecting the baseline data will take approximately 10 minutes.
- The possible, but unlikely, unfavorable outcome of elective resection.
9.4 **Compensation for injury**

The Meander Medical Center has taken out a liability insurance policy with Medirisk.

- Damage sustained during the experiments (physical damage or death) or revealing within 5 years after the experiments is insured.
- The insurance covers the damage up to an amount of € 450.000 per subject and up to € 3.500.000 for damage sustained by all research subjects participating in this study together.
- For all the research done at the Meander Medical Center the insured amount is maximized up to € 5.000.000 per insurance year.
- In case of personal damage, the research subject has the right to contact the insurance company directly or via a liaison (see below). The subject is requested to contact the research coordinator and the section of legal affairs.

10. **ADMINISTRATIVE ASPECTS AND PUBLICATION**

10.1 **Handling and storage of data and documents**

All the questionnaires are collected by the research coordinator and stored in a cupboard that can be locked.

A professional datamanager will be used for the datamanagement of this clinical trial. All data used for statistical analysis are stored in a SPSS® database. Data will be stored and used anonymously and the anonymisation key will be only accessible to the research coordinator. The patient information in the chart will be kept in the medical archive for 15 years.
10.2 Amendments

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

10.3 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.

10.4 End of study report

The investigator will notify the accredited METC of the end of the study within a period of 8 weeks.

In case the study is ended prematurely, the investigator will notify the accredited METC, 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.
REFERENCES


### 12.1 Tabel Hinchey Classification

<table>
<thead>
<tr>
<th>Hinchey Classification</th>
<th>Modified Hinchey Classification</th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>Mild clinical diverticulitis</td>
<td>LLQ pain, elevated WBC, fever, no confirmation by imaging or surgery</td>
</tr>
<tr>
<td>I</td>
<td>Pericolic abscess or phlegmon</td>
<td>Ia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ib</td>
</tr>
<tr>
<td>II</td>
<td>Pelvic, intraabdominal, or retroperitoneal abscess</td>
<td>II</td>
</tr>
<tr>
<td>III</td>
<td>Generalised purulent peritonitis</td>
<td>III</td>
</tr>
<tr>
<td>IV</td>
<td>Generalized fecal peritonitis</td>
<td>IV</td>
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### 12.2 Ambrosetti Classification

<table>
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<th>Ambrosetti Classification</th>
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<tr>
<td>Mild</td>
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| Thickening of bowel wall ≥5mm and Inflammation of pericolic fat | Bowel wall thickening ≥ 5mm and Inflammation of pericolic fat _in combination with:_
|                            | • Abcess and/or
|                            | • Extraluminal air/contrast |
12.3 Flow chart design

Patients with persisting abdominal complaints after an episode of diverticulitis and/or frequently recurring diverticulitis
N= 214

Bowel wall thickening with or without abscess on recent radiological examination

Conservative management

Informed consent

Baseline
- GIQLI, SF-36, EQ-5D, ROME III and costs questionnaires
- Assessment medical status

RANDOMISATION

Elective resection
Continuation conservative treatment

3,6,9,12,24 and 36 months
- GIQLI, SF-36, EQ-5D, ROME III and VAS
- Costs & event assessment questionnaire