Laparoscopic Lavage

A Paradigm Shift for the Treatment of Perforated Diverticulitis with Purulent Peritonitis?

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To my family,
both the biological and the other one

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ABSTRACT

Introduction
Perforated diverticulitis of the colon is a condition that sometimes requires surgical treatment. Traditionally Hartmann's procedure is the recommended treatment. Laparoscopic lavage has lately evoked interest as a definite treatment for perforated diverticulitis with purulent peritonitis.

Aim
To evaluate the surgical treatment for perforated diverticulitis and to assess laparoscopic lavage as a definite treatment for perforated diverticulitis with purulent peritonitis.

Patients and Methods
Paper I explores the morbidity and mortality of patients operated due to perforated diverticulitis at Sahlgrenska University Hospital 2003 to 2008. Papers II-IV describe the conception, structure and the results of the randomised controlled trial DILALA, which compares laparoscopic lavage to Hartmann's procedure as a treatment for perforated diverticulitis with purulent peritonitis.

Results
Paper I found that 44% of the patients were re-operated after surgical treatment for perforated diverticulitis. The mortality rate during first admission was 6%. The stoma, a result from Hartmann's procedure, became permanent in 40% of the patients. The DILALA-trial showed that for laparoscopic lavage 28% were re-operated compared to 63% for the Hartmann's procedure, a relative risk reduction of 59% for re-operation (RR 0.41, 95% CI 0.23-0.72) (p=0.004) There was also significantly shorter operating time and shorter length of hospital stay. No differences were found in mortality, morbidity or quality of life.

Conclusion
The scientific evidence for laparoscopic lavage is still limited but our results indicate that laparoscopic lavage is superior to Hartmann's procedure when treating perforated diverticulitis with purulent peritonitis.

Keywords: diverticulitis, acute, Hartmann, laparoscopy, lavage

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SAMMANFATTNING PÅ SVENSKA

Tjocktarmsfickor (kolondivertiklar) är vanligt förekommande i den västerländska befolkningen. Förekomsten ökar med ålder och beräknas till ungefär 5-10% bland 40-åringar, och 50% bland 70-åringar. Omkring en femtedel utvecklar symtom ifrån sina divertiklar varvid det benämns divertikelsjukdom. Denna kan delas in i icke-inflammatorisk sjukdom som kan yttra sig i form av i blödning, smärta och ändrade avföringsvanor, och inflammatorisk sjukdom som kallas divertikulit.

Divertikulit drabbar ca 20% av patienter med divertikelsjukdom. Divertikulitepisoderna har mestadels ett okomplicerat förlopp där smärtlindring och skonkost ofta är tillräcklig behandling. Ibland förvärras symtomen vilket kan kräva inneliggande observation, antibiotikabehandling och operation. I den mer komplicerade formen av divertikulit kan en bristning av tarmen uppstå (perforation). Perforationens utbredning beskrevs klassificerades på 70-talet av Hinchey enligt grad I-IV. Hinchey grad I och II är perforationer som inneslutits i en omgivande varböld (abscess) och som kan behandlas med antibiotika och ibland ultraljudsledd punktion med dränage. Hinchey grad III (varig bukhinneinflammation) och grad IV (avföring i fri bukhåla) kräver akut operation.

Traditionellt har Hartmanns operation varit det rekommenderade ingreppet vid Hinchey III och IV. Vid denna operation öppnar man buken och tar bort (resecerar) det segment av tjocktarmen som har perforerat och sluter sedan det kvarvarande tarmpartiet nedom resektionen. Därefter lägger man upp den övre tarmändan som en påse på magen (stomi). Efter att patienten har läkt och hämtat sig från detta ingrepp kan man vid ytterligare en operation lägga ner stomin och koppla samman tjocktarmen förutsatt att patienten önskar detta och är vid tillräckligt god hälsa.

Hartmanns operation är behäftad med komplikationer såsom infektion, sårruptur, ärrbråck, stomibråck samt en icke obetydlig dödlighet. 1996 publicerade O'Sullivan en artikel i vilken en metod beskrevs där tarmresektion undveks och även visade på fördelaktiga resultat avseende komplikationer. Denna metod bestod i att man med hjälp av titthålsteknik (laparoskopi) sköljde (lavage) det inflammerade området hos patienter med Hinchey grad III. Metoden kallas laparoskopisk lavage. Därefter anlägger man en dränslang och fortsätter med antibiotikabehandling med avsikten att undvika öppen operation, tarmresektion och stomi. Även efterföljande studier rapporterade fördelar med metoden, men intresset intensifierades

först 2008 då Meyers publicerade resultat från en stor icke-randomiserad, icke-kontrollerad, prospektiv multicenter studie.

För att kunna introducera en ny behandling krävs vetenskapliga bevis (evidens). Från O'Sullivans artikel och fram till 2014 fanns endast resultat från fallserier och icke-randomiserade studier avseende laparoskopisk lavage för perforerad divertikulit Hinchey grad III, vilket inte ger starka vetenskapliga bevis. Inga randomiserade studier hade ännu publicerats.

Denna avhandlings ändamål var att kartlägga effekterna av den kirurgiska behandlingen av perforerad divertikulit bland patienter på Sahlgrenska Universitetssjukhuset mellan 2003 till 2008, samt att fastställa huruvida det förelåg vinster med att behandla patienter med perforerad divertikulit Hinchey grad III med laparoskopisk lavage istället för med Hartmanns operation.

I det första delarbetet analyserades alla patienter på Sahlgrenska Universitetssjukhuset som mellan 2003 och 2008 hade diagnosen perforerad divertikulit vid utskrivning och som opererats akut under vårdtillfället. Vi såg till antalet re-operationer och inkluderade även elektiva ingrepp såsom stominedläggning och ärrbråck, och fann att 44% av patienterna re-opererades. Sex procent avled vi första vårdtillfället och 40% hade kvarvarande stomi.

Då laparoskopisk lavage hade visat resultat på omkring 5% re-opererade patienter samt en dödlighet på 3% föreföll det rimligt att i en randomiserad, kontrollerad studie för att värdera denna metod. Det var mot denna bakgrund DILALA-studien initierades.

I det andra delarbetet beskrivs strukturen till DILALA-studien. Studien är en randomiserad, kontrollerad multicenter-studie där patienterna med perforerad divertikulit Hinchey grad III genomgick traditionell Hartmanns operation (kontrollgrupp) eller till laparoskopisk lavage (intervention). Studien utfördes på fyra sjukhus i Sverige och fem sjukhus i Danmark. Huvudfrågeställningen (primära effektmåttet) var andel patienter som genomgått en eller flera re-operationer inom 12 månader efter den initiala akutoperationen. DILALA inkluderade patienter från februari 2010 till februari 2014.

I delarbete 3 och 4 presenteras resultaten från DILALA-studien. Vi fann kortare operationstid, kortare tid på uppvakningsavdelning och kortare vårdtid för laparoskopisk lavage. Tillika fann vi att andelen patienter som re-

opererats efter att ha genomgått laparoskopisk lavage var 28% jämfört med 63% för Hartmanns operation. Denna skillnad var också statistiskt säkerhetsställd (signifikant). Det förelåg inga skillnader i komplikationer eller i dödlighet mellan de två behandlingarna.

Sammanfattningsvis fann vi att efter behandling med Hartmanns operation för perforerad divertikulit föreligger en betydande risk för re-operation, en ej obetydlig dödlighet och 40% av patienterna erhåller en permanent stomi. Laparoskopisk lavage som behandling vid perforerad divertikulit Hinchey III reducerar risken för att re-opereras med 60% och minskar vårdbehovet.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. **Perforated diverticulitis operated at Sahlgrenska University Hospital 2003-2008**
Thornell A, Angenete E and Haglind E. *Dan Med Bull*, 2011. 58(1): p. A4173.

II. **Treatment of acute diverticulitis laparoscopic lavage vs. resection (DILALA): study protocol for a randomised controlled trial**
Thornell A, Angenete A Gonzales E, Heath J, Jess P, Läckberg Z, Ovesen H, Rosenberg J, Skullman S and Haglind E. *Trials*, 2011. 12: p. 186.

III. **Laparoscopic Lavage Is Feasible and Safe for the Treatment of Perforated Diverticulitis With Purulent Peritonitis: The First Results From the Randomized Controlled Trial DILALA**
Angenete E, Thornell A, Burcharth J, Pommergaard H-C, Skullman S, Bisgaard T, Jess P, Läckberg Z, Matthiessen P, Heath J, Rosenberg J, Haglind E. *Ann Surg*. 2014 Dec 8. [Epub ahead of print]

IV. **Laparoscopic lavage as treatment for perforated diverticulitis with purulent peritonitis (DILALA): a randomized controlled trial**
Thornell, A, Angenete E, Bisgaard T, Bock D, Burcharth J, Heath J, Pommergaard H-C, Rosenberg J, Stilling N, Skullman S, Haglind E. *Annals of Internal Medicine,* Accepted October, 2015

CONTENT

ABBREVATIONS

SF-36	Short-Form 36 Health Survey
VAS	Visual Analogue Scale
KPP	Svenska Kommuner och Landstings register för Kostnad Per Patient (Swedish Association of Local Authorities and Regions Registry for Cost per Patient Registry)
ICD	International Statistical Classification of Diseases and Related Health Problems
NOMESCO	Nordiska Medicinalstatistiska Kommittén (Nordic Committee for Medical Statistics)
CRF	Clinical Record Form
EORTC-QLQ-C30	European Organisation for Research and Treatment of Cancer-Quality of life Questionnaire-Cancer 30
EORTC-QLQ-CR28	European Organisation for Research and Treatment of Cancer-Quality of life Questionnaire-Colorectal 28
ASA	American Society of Anesthesiologists
BMI	Body Mass Index
RR	Relative Risk
CI	Confidence Interval
SD	Standard Deviation
FWER	Family-Wise Error Rate
Q1;Q3	Upper (1) and lower (3) quartile (Q)

1 INTRODUCTION

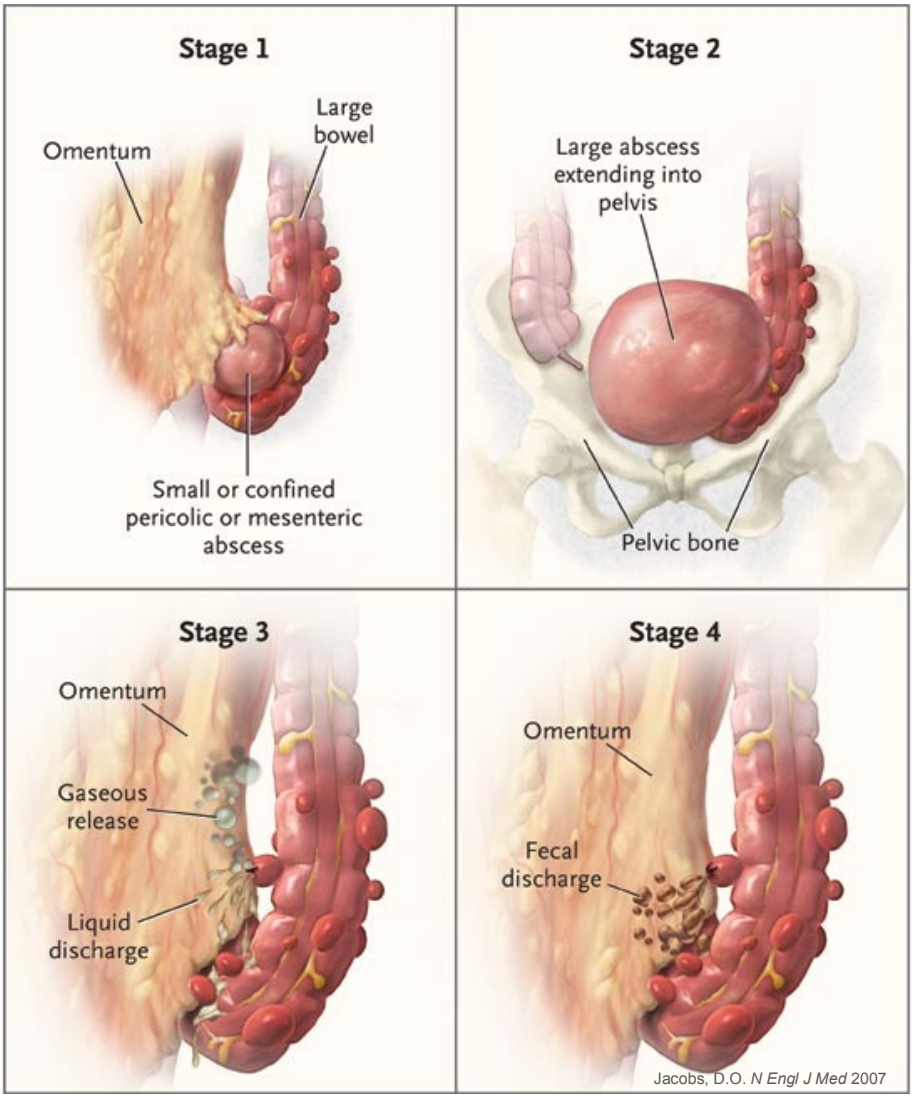
1.1 Diverticulitis

The term diverticulosis describes the presence of a colonic diverticulum, which is a common finding in the Western population. Colonic diverticula are seen in around 10% of the population around 40 years of age and increases with age to reach 50% and more in people over 70 years[1,2]. If symptoms from colonic diverticula occurs it is referred to as diverticular disease, which is seen in about 20% of patients with colonic diverticula. This can be categorised into non-inflammatory disease and inflammatory disease. The symptoms of non-inflammatory diverticular disease often present themselves as altered bowel habits, visceral hypersensitivity and bleeding[3-5].

The inflammatory diverticular disease is termed diverticulitis. The true incidence is unclear but it is estimated to occur in 20% of the population with diverticular disease[4]. It is commonly divided into uncomplicated and complicated disease. Uncomplicated diverticulitis can often be treated conservatively with symptomatic treatment in an outpatient setting (pain medication and bowel rest), whereas complicated diverticulitis may require admission, antibiotics and surgery[6].

The precise pathophysiology of acute diverticulitis is unknown, but is has been suggested that when faecal matter obstructs the narrow neck of a diverticulum it may cause bacterial overgrowth, distension of the sack and ischemia. This weakens the wall of the diverticulum, which may lead to perforation[5]. There severity of perforated diverticulitis can be categorised according to several different scales, but the most frequently used is the Hinchey classification[7,8] (**Figure 1**).

Figure 1. The Hinchey Classification

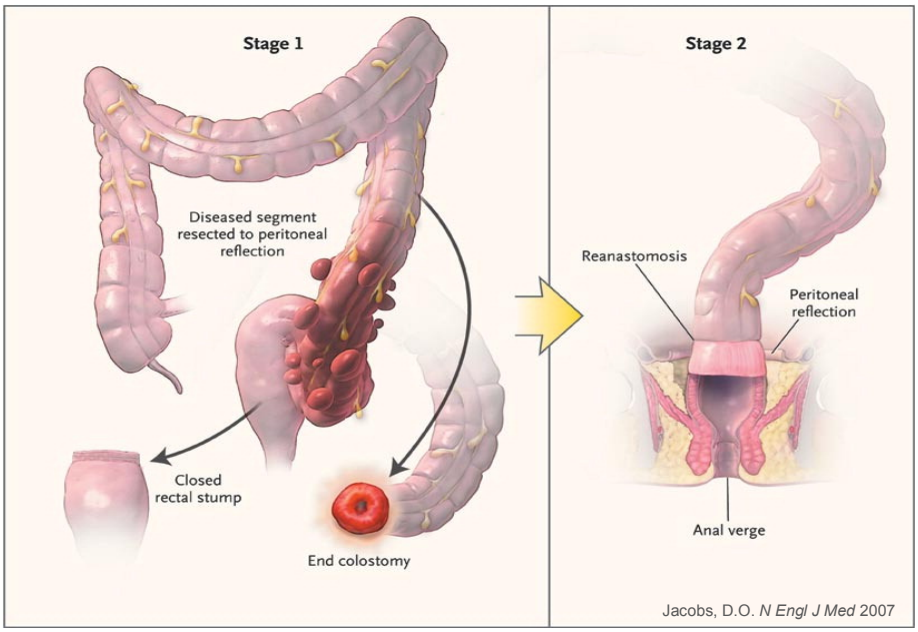


At the time Hinchey presented his classification system it was based on peri-operative findings, but with the development of radiology stage I and II can now be diagnosed, and treated when needed (draining of abscess), without laparotomy. The distinction between stage III (purulent peritonitis) and IV (faecal peritonitis) is difficult without macroscopic overview. This overview can be attained with laparoscopy thus avoiding a laparotomy.

1.2 Surgical treatment

Hartmann's procedure has historically been the gold standard procedure for treating perforated diverticulitis Hinchey stage III and IV[9]. During this operation the inflamed segment of the colon is resected, the distal stump is closed and a stoma is formed. The stoma can be reversed in a second operation at a later stage (**Figure 2**). Hartmann's procedure, however, entails complications with mortality reported to be as high as 20% and morbidity of around 40%[10,11]. Not only is the primary operation a procedure with substantial morbidity and considerable mortality, the stoma reversal also can lead to complications such as leakage in the anastomosis, abscess and wound infection. Moreover, approximately 40% of patients do not undergo the reversal procedure and consequently have a permanent stoma[12-14].

Figure 2. Stage 1: Hartmann's Procedure, Stage 2: Stoma Reversal



Resection with a direct restoration of bowel continuity, primary anastomosis, is another surgical strategy for managing perforated diverticulitis. This procedure can be performed with or without a temporary protective proximal stoma; an ileostomy. The advantage is the avoidance of a colostomy that needs to be reversed in a second laparotomy, but there is an inherent risk of anastomotic leakage. The reversal of an ileostomy is a procedure often not requiring laparotomy and considered less complicated,

but it is nevertheless an operation with considerable morbidity[15]. Primary anastomosis, with or without protecting ileostomy, shows beneficial results to Hartmann's procedure but the evidence is still of low grade[12,16].

In 1996 O'Sullivan et al described a technique where perforated diverticulitis with purulent peritonitis was treated by a laparoscopic procedure irrigating the abdomen with saline without resection of the diseased sigmoid segment[17]. Several prospective and retrospective reports have been presented since then but in 2008 Meyers et al published a large prospective, multi-centre, non-controlled consecutive cohort study with promising results showing low morbidity and mortality[18]. This started an intensified interest in laparoscopic lavage and several randomised controlled trials were initiated (the Ladies Trial[19], SCANDIV[20], LapLand[21] and DILALA[22]). So far three of these randomised controlled trials have published results[23-25].

1.3 Health related quality of life

The results of surgical procedures are traditionally measured mainly by morbidity and mortality. Nevertheless, research show increased mortality in patients with poor self-assessed quality of life[26] and surgical research therefore has an increasing interest in the physical and the mental well being of the individual patient.

There are indications that patients operated on with elective sigmoidectomy due to recurrent diverticulitis report an improved quality of life postoperatively[27,28]. But for patients operated on under emergency conditions due to perforated diverticulitis no quality of life studies have been published[29]. There is also no existing specific instrument that encapsulates the quality of life of a patient with acute perforated diverticulitis, which perhaps explains the absence of study results. In the DILALA-trial we used the generic instruments Short Form (36) Health Survey[30] and EuroQol-5D[31,32] and the validated Swedish and Danish translations[33-35].

2 AIM

The overall aim of this thesis is to evaluate the effects of surgical treatment for perforated diverticulitis.

Specific aims were:

- Describe the results of the surgical treatment for perforated diverticulitis in a retrospective, consecutive series of patients at Sahlgrenska University Hospital.
- Determine whether laparoscopic lavage results in fewer re-operations than Hartmann's procedure.
- Explore differences in re-admissions and the length of hospital stay between the two modalities.
- Assess the mortality and adverse events of Hartmann's procedure compared to laparoscopic lavage.
- Evaluate the quality of life after surgery for perforated diverticulitis.

3 TRIAL DESIGNS

In order to meet the aims of this thesis two studies were conducted. First we reviewed the existing studies of patients operated for perforated diverticulitis and found few recent studies, most with small sample sizes[9]. We therefore decided to perform a retrospective study to receive updated data and to specifically emphasise on patient suffering and resource consumption. The results were used as a foundation for a randomised controlled trial to explore the outcome of laparoscopic lavage versus Hartmann's procedure in perforated diverticulitis with purulent peritonitis.

3.1 Identifying the problem

Surgical procedures are constantly refined with the purpose of increasing survival and reducing morbidity. After being introduced more than 90 years ago, Hartmann's procedure is still a viable option for certain surgical situations. However, there is no surgery without consequences.

Prior to recommendation of an alternative treatment modality scientific evidence provided in clinical studies is required. At the time of the design of the DILALA-trial in 2009 the existing reports for laparoscopic lavage were case series, prospective studies and retrospective studies. A randomised controlled study with Hartmann's procedure as control and laparoscopic lavage as intervention had so far not been initiated.

3.2 The retrospective study

The aim of the retrospective study was to evaluate the effects of surgical treatment of perforated diverticulitis and to serve as a basis for a randomised controlled trial.

We decided to perform a retrospective review of the documentation for all patients operated on due to perforated diverticulitis at Sahlgrenska University Hospital within a recent five-year period to obtain the most accurate data as possible regarding morbidity and mortality.

Consecutive patients with emergency admission and the ICD diagnosis code; K573 (perforated diverticulitis with perforation or abscess) and K572 (perforated diverticulitis without perforation or abscess) were identified from the Cost Per Patient registry (KPP database). In order to verify that

they were also operated on due to their diverticulitis a search for operations under Chapter J in the Nordic Committee for Medical Statistics database (NOMESCO) was performed. Data was then collected from their medical records. The patient baseline included co-morbidity, which was defined as cancer, cardio-vascular disease, chronic obstructive pulmonary disease and treatment with immuno-modulating drugs. The outcomes studied were re-operations, re-admittance, length of hospital stay and permanent stoma. Patients with other diagnosis than perforated diverticulitis were excluded from the analysis.

3.3 The randomised trial

The randomised controlled trial DILALA began its inclusion in February 2010. It was a multicentre trial recruiting patients from hospitals of various sizes in Denmark and Sweden. The aim was to compare Hartmann's procedure with laparoscopic lavage as treatment for patients with perforated diverticulitis with purulent peritonitis.

3.3.1 Evidence based surgery

Establishing scientific evidence is a slow and difficult process. By assessing available studies the strength of the evidence can be graded. In the hierarchy of evidence the opinion or the idea of a certain treatment holds the lowest grade of evidence and a systematic review the highest. Case-reports, retrospective and prospective studies contribute to the evidence to a certain degree and are important when forming a hypothesis for a randomised controlled study. The quality of the systematic review is dependent of the quality of the reviewed studies. The more high quality randomised controlled trials available for review, the higher grade of evidence[36,37].

3.3.2 External validity

A key quality in a clinical randomised trial is the extent to which the results can be generalised. The optimum is a study population as similar as possible to the unselected population who have had the same disease.

Measures such as broad inclusion (few exclusion criteria, multicentre design and multinational recruitment), using well-defined randomisation procedures, allocation concealment and registration of excluded and non-included patients can be used to determine generalisability.

If there are a large number of eligible non-included patients it can be an indication of a selection bias resulting in a misleading result. The study outcome may then not be applicable to a general population.

3.3.3 Multicentre design

The advantage of a multicentre study is increased generalisability. A design that involves multiple investigators decreases potential bias by diluting the impact of local or individual preferences. The greater number of centres participating the smaller the risk of a single centre causing bias. A multicentre study also creates an opportunity to recruit subjects from a wider population base. The DILALA-trial was a multicentre trial conducted in Denmark and Sweden.

We decided to include hospitals of different sizes. Perforated diverticulitis is an emergency condition and sometimes surgery cannot wait until a colorectal surgeon is available. Therefore all surgeons managing acute patients must be able to handle such a condition. By including hospitals without a colorectal surgeon available at all time to perform the surgery the clinical reality is reflected in a higher degree.

A multicentre study enables recruitment from a larger population, thereby increasing the accrual rate. Slow recruitment for a clinical trial is problematic in several respects. With a long trial period there is a risk that the results will be out-dated due to altered guidelines, technical advances or new medications. Also, important study results, useful for patients and health-care providers, might not be shared in a timely fashion.

There are disadvantages with a multicentre study that involves a great number of people in different locations, sometimes in different countries. Staying in contact and motivating multiple departments to keep up the good work for the duration of the study is a difficult task. The language barrier requires thorough consideration regarding the translation of clinical record forms, questionnaires, consent forms etc. A multicentre study is also more expensive, requiring adequate funding from the onset.

3.3.4 Randomisation and blinding

Randomisation is used to prevent researchers, health care staff and patients predicting or influencing the allocation. Ideally a randomised study is also blinded to both staff and subject, but in a clinical trial involving surgery this is often impractical or impossible.

Permuted blocks (or block stratification) were used in the DILALA-trial to ensure an even distribution between groups without disclosing allocation. In a trial cohort consisting of 50 patients where there are 25 envelopes for treatment A and 25 envelopes for treatment B this can be done as follows. If the cohort is divided into blocks of 4 with two envelopes for each treatment in every block. By re-mixing them after every fourth patient, the randomisation distribution will be 50% in each group. If the participation of a centre is interrupted or if the study is discontinued before full inclusion is reached an even allocation distribution is still attained.

The DILALA-trial did not allow blinding either to staff or patient due to the different surgical approaches between laparoscopic lavage and Hartmann's procedure. Therefore it was conducted as an open-label randomised controlled trial, where the allocation sequence was computer generated by the trial group statistician and concealed to the staff in opaque sealed envelopes. Allocation was revealed only after the initial diagnostic laparoscopy showed perforated diverticulitis with purulent peritonitis. The envelopes were sent to the participating centres in blocks of 10 patients per block and were not stratified according to hospital size.

3.4 Primary endpoint

The primary endpoint in the DILALA-trial was the percentage of patients with one or more re-operation within 12 months from the emergency operation.

A number of considerations need to be taken into account when deciding a primary endpoint for a clinical randomised study, but the primary focus needs to be of clinical or biological importance to either the individual patient, the health care provider or to society in general, preferably all three.

A need for a re-operation often reflects a complication. This may not only increase patient suffering but also prolong the hospital stay. However, when choosing Hartmann's procedure as the treatment for perforated diverticulitis the stoma reversal follows as an elective operation in some 60%[14]. Surgeons may not always consider this procedure to be as a re-operation *per se* by, but it is certainly a considerable procedure for the individual and an operation with complications causing increased resource consumption[10,13,29]. For this reason the reversal of the stoma was included as a re-operation in the DILALA trial.

3.5 Secondary endpoints

3.5.1 Re-operations, re-admissions and length of hospital stay

We chose the mean number of re-operations as a secondary outcome. The rate of re-operations can to some extent reveal whether the treatment modality is definite or not, but will not fully reveal the extent of care needed by the patient. Therefore re-admissions were included as a secondary endpoint, together with the cumulative length of hospital stay.

3.5.2 Adverse events

Post-operative adverse events were collected in the CRF as separate events, documenting the exact nature, date and duration of each event. In 2014 when full inclusion was attained we decided to use the Clavien-Dindo classification to facilitate comparison with other studies. Initially this was not part of the protocol because at the time of the trial design the 5-year validation of this classification system had not been published[38].

The Clavien-Dindo classification consist of five grades, where both grade III and IV are split into 'a' and 'b' sub-groups. Grade V is the death of the patient and often not presented as a complication but categorised as mortality in surgical trials.

Grade I and II are mild complications that may (II) or may not (I) require pharmacological treatment. The retrospective classification performed in the DILALA-trial proved to be difficult regarding grade I and II. After some consideration we decided to combine grade I and II to reduce the risk of misclassification.

Grade III is an adverse event with the need for surgical, endoscopic or radiological intervention. The distinction between grade IIIa and IIIb is the need for general anaesthesia during intervention (IIIb).

Grade IV is a life threatening adverse event requiring management in the intensive care unit where IVa is single organ failure and IVb is multiple organ failure.

We classified adverse events according to Clavien-Dindo at 30 and 90 days and the results are presented in Papers III and IV, respectively. The reason for not to record adverse events for 12 months is that the longer time passing between the initial acute operation and the adverse event, the more

difficult it is to decide if the complication is causally related to the primary condition.

3.5.3 Mortality

All randomised patients who died within 12 months were registered as mortality, and the data was obtained from the Clinical Register Form (CRF) regardless of cause of death.

Based on the number of patients who died in the retrospective study (6 out of 106 patients) we decided not to use mortality as a primary endpoint. To provide conclusive results with such a rare event would not be feasible.

3.5.4 Stoma at 12 months

We considered it an important endpoint if a patient had a stoma at 12 months. This would indicate either that a reversal procedure had not been undertaken or that the patient had experienced an adverse event requiring the formation of a stoma. A stoma may also decreases quality of life[29].

3.5.5 Quality of life

There are no disease specific quality of life instruments for acute perforated diverticulitis and studies of the quality of life of patients with diverticular disease are limited. Most available data present quality of life for uncomplicated diverticulitis or after elective surgery due to chronic diverticular disease[39]. It was therefore decided to use the generic instrument EuroQol-5D[31,32] and Short-Form 36 Health Survey (SF-36)[30]. In addition we used selected parts of the European Organisation for Research and Treatment of Cancer-Quality of life Questionnaire-30 (EORTC-QLQ-C30) and the European Organisation for Research and Treatment of Cancer-Quality of life Questionnaire-Colorectal 38 (EORTC-QLQ-CR38) (**Appendix**). The patients were asked to answer the questionnaire at discharge, 6 months and at 12 months.

Spiegel et al[40] recently presented an instrument specifically for diverticular disease, DV-QoL. This instrument focuses mainly on chronic disease rather than acute, but could be considered for future studies on the subject.

3.6 Statistical considerations

The power calculation in the DILALA-trial was based on the assumption to reduce re-operations from 40% to 10% of the patients. These estimates

were based on the results from Paper I[14] and the results from Meyers et al[18]. Such reduction would be detected with 80% power using a 2-sided statistical test with 5% significance level and 32 evaluable patients per group.

Initially the primary analysis was based on a per protocol population, i.e. patients excluded due to other diagnoses such as colorectal cancer or gynaecological infection. However, we decided to perform an analysis consisting of all randomised patients. This cohort reflects the clinical reality where difficulties in diagnosing patients sometimes can result in patients with diagnoses other than Hinchey III undergo laparoscopic lavage.

If a patient prematurely terminates their participation in a study it will give rise to missing data and censoring. In the DILALA-trial we did not believe missing data to be a serious concern. First, there were no major discrepancies between the groups regarding the follow-up time. Secondly, an operation is performed once as opposed to continuous medication, we therefore expected serious harm to be detected relatively early. If a patient dies or terminates participation, the information on further possible re-operations will not be collected. It would therefore be favourable to a group if there were a high dropout rate or high mortality early in the trial. Such inter-patient differences in follow-up time were corrected for by including an offset-variable in the statistical model. An offset-variable takes into account whether or not a patient has a long or short follow-up causing differences in time at risk for example adverse events. Contingencies of all patients within 12 months will hence be accounted for.

The authenticity of a trial must always be tested to dismiss the possibility of a result being generated by chance. When a single statistical hypothesis test is performed, the risk of incorrectly rejecting a true null hypothesis (type I error) is fixed at a significance level, for example 5%. When several tests are made there is consequently an increased risk of making at least one type I error. This is referred to as the family-wise error rate (FWER) and will be higher than the nominal significance level. In the DILALA-trial the FWER was controlled by a parallel Bonferroni gatekeeping procedure[41]. In this procedure groups of different statistical hypotheses are formed and thereafter ordered. The hypotheses in the family of highest order are first tested. Only if at least one of the hypotheses is rejected, the hypotheses of the lower order groups are tested.

3.7 Ethical considerations

The DILALA-trial was approved by the Swedish (EPN/Göteborg Dnr 378-09) and the Danish (Protocol nr. H-4-2009-088) ethics committee.

Patients with perforated diverticulitis are often in a septic or pre-septic condition and it is not uncommon for a septic patient to have an impaired cognitive function, therefore the Swedish ethics committee decided that for patients who were incapable of giving informed consent in an emergency setting it was sufficient to inform the relatives. When the patient was recovering after the surgical procedure a formal consent was acquired. Informed consent was collected in all other cases.

The trial was registered at ISRCTN for clinical trials ISRCTN82208287 (http://www.controlled-trials.com/ ISRCTN82208287).

4 RESULTS

4.1 Paper I

All patients diagnosed with perforated diverticulitis (ICD-code K57.2 and K57.3) and operated on with colonic resection (NOMESCO chapter J) at Sahlgrenska University Hospital, between 1 January 2003 and 30 June 2008 were collected. The follow-up period was ended on 1 June 2009.

A total of 106 patients underwent colonic resection due to perforated diverticulitis, of these 77% underwent Hartmann's procedure and 23% underwent colon resection with primary anastomosis.

During the first hospital stay 12% of the patients were re-operated once and 6% were re-operated more than once. The mean number of re-operations per patient was 0.3 (range 1-10). Including elective procedures, 44% of the patients were re-operated during a later admission (**Table 1**).

Mean length of hospital stay for the acute admission was 17 days (median 12 [range 1-111]) (**Table 1**).

Of the patients who underwent Hartmann's procedure 43% did not have stoma reversal at the end of follow-up.

Six patients (6%) died during the follow-up period.

Table 1. Retrospective study outcome data

	Men (n=51)	*Women (n=55)*	*Total (n=106)*
Age - mean (SD)	58 (15.5)	74 (12.4)	65 (15.3)
*Re-operated patients - n (%)**	30 (59%)	17 (31%)	47 (44%)
Re-operated ≥1 during first admission - n (%)	11 (22%)	8 (15%)	19 (18%)
Length of hospital stay - mean/median (range)	18/10	17/13	17/12 (1-111)
Mortality during first admission - n (%)	1 (2%)	5 (9%)	6 (6%)

*Total number of re-operated patients is 47 (44%). Incorrect number presented in article.

The heading of table 2 is misguiding because it refers to the number of re-operations but the results presents the number of re-operated patients.

There is also a numerical fault in this table. The total number of re-operated patients is 47 (44%).

The sentence “the rate of reoperations at readmission was 43%” is incorrect and should have been removed.

4.2 Paper II

This paper describes the background and the design of the DILALA-trial. No results are included.

The primary endpoint is described in Paper II as “the number of re-operations within 12 months from the initial emergency operation”. However, the correct primary endpoint is: the percentage of patients with one or more re-operations within 12 months from the initial emergency operation.

4.3 Paper III

In the third paper we presented the 30-day results of the DILALA-trial. After randomisation there were 83 patients. We analysed the cohort after per-protocol exclusions, which resulted in a total of 75 patients. Of these 39 patients were randomised to laparoscopic lavage (laparoscopic group) and 36 patients to Hartmann’s procedure (Hartmann group).

The laparoscopic group had a shorter median operating time (68 minutes [range 28-194]) compared to the Hartmann group (154 minutes [range 58-266 min]) ($p<0.001$). Median time in the recovery unit was shorter for the laparoscopic group (4 hours [range 1-12]) than for the Hartmann group (6 hours [range 2-44]) ($p=0.045$). In the laparoscopic group median hospital stay was 6 days (range 2-27) compared to 9 days (range 4-36) to the Hartmann group ($p=0.037$) (**Table 2**).

The Clavien-Dindo classification showed no statistical significant differences. The 30-day mortality was 3 (8%) in the laparoscopic group and no deaths in the Hartmann group. After 90-days the number of deaths had not changed for the lavage group but had increased to 4 (11%) in the Hartmann group, with no statistically significant difference.

Table 2. Short-term outcome data

	Laparoscopic Lavage n=39	*Hartmann's Procedure n=36*	*p*
Duration of surgery - hh:mm (range)	1:08 (0:28-3:14)	2:34 (0:58-4:26)	<0.001
Time in recovery unit - hours (range)	4 (1-12)	6 (2-44)	0.045
Postoperative hospital stay - days (range)	6 (2-27)	9 (4-36)	0.037
Mortality within 30 days - n (%)	3 (8%)	0	ns
Mortality within 90 days - n (%)	3 (8%)	4 (11%)	ns

In the lavage group 5 patients (13%) were re-operated within 30 days after the initial acute operation compared to 6 patients (17%) in the Hartmann group.

4.4 Paper IV

This paper presents the primary and secondary outcome variables at twelve months. The analysis was conducted as intention-to-treat including all randomised patients.

Out of a total of 139 enrolled patients undergoing diagnostic laparoscopy, 83 were found to have a perforated diverticulitis with purulent peritonitis. Of these 43 were randomised to laparoscopic lavage (laparoscopic group) and 40 to Hartmann's procedure (Hartmann group). After the per-protocol exclusions there were 38 patients in the laparoscopic group and 35 in the Hartman group. A secondary per-protocol cohort was also analysed, where patients with exclusion criteria after randomisation, as specified in the trial protocol, were excluded. The reasons for exclusion were: colorectal cancer (4), small bowel perforation (1), small bowel obstruction with ischemia (1), gynaecological infection (1) and one sigmoid resection with primary anastomosis (a procedure not included in this trial). One patient withdrew consent and one patient declined further active participation.

No obvious differences were detected between the lavage group and the Hartmann group regarding age, sex, American Society of Anesthesiologists classification (ASA), Body Mass Index (BMI) or comorbidity in the intention-to-treat analysis or in the per-protocol analysis.

Table 3. Primary and Secondary outcomes of the DILALA-trial

	Laparoscopic Lavage n=43	*Hartmann's Procedure n=40*	*Relative Risk laparoscopic lavage versus Hartmann's procedure (95% CI)*	*Adjusted p-value**
Percentage of patients with one or more re-operations - % (SD)	27.9% (44.9%)	62.5% (48.4%)	0.41 (0.23 to 0.72)	0.004
Mean number of re-operations per patient - mean (SD)	035 (0.61)	0.80 (0.91)	0.40 (0.22 to 0.76)	0.010
Patients with no re-operation - n (%)	31 (72%)	15 (38%)		
Total length of hospital stay - mean (SD); median (Q1;Q3)	14 (13); 8 (5;21)	18 (22); 14 (9;21)	0.65 (0.45 to 0.94)	0.047
Stoma at 12 months - n (%)	3 (7%)	11 (28%)		
Mortality - n (%)	6 (14%)	6 (15%)		

*Adjusted for the family-wise error

Analysis of the primary endpoint revealed that 28% of the patients in the laparoscopic group underwent a re-operation compared to 63% in the Hartmann group, a relative risk reduction for a re-operation of 59% in the laparoscopic group (RR 0.41, 95% CI 0.23 to 0.72) (p=0.004). Moreover, the mean number of re-operations in the laparoscopic group (0.35 [SD 0.61]) was significantly lower than in the Hartmann group (0.80 [SD 0.91]) (p=0.01) (**Table 3**). Two patients in the laparoscopic group were re-operated with Hartmann's procedure, one due to abscess and one due to faecal leakage in the drainage.

Four patients were diagnosed with cancer, three in the laparoscopic group and one in the Hartmann group.

The total mean length of hospital stay within 12 months was 14 days (SD 13) in the laparoscopic group and 18 days (SD 22) in the Hartmann group (RR 0.65, 95% CI 0.45 to 0.94) (p=0.047) (**Table 3**). Sixteen percent were re-admitted in the laparoscopic group due to recurrent diverticulitis.

After 90 days there were no significant differences in adverse events between the groups measured by using the Clavien-Dindo classification.

Twelve patients died (6 patients in the laparoscopic group and 6 patients in the Hartmann group), where two patients in each group died from failure to control the septic condition after the primary emergency operation.

At twelve months three patients in the laparoscopic group (7%) had a stoma compared to 11 patients (28%) in the Hartmann group. (**Table 3**).

No differences were seen between groups in either EuroQol-5D or SF-36. Both instruments reflected low quality of life at discharge and an improvement by 12 months. In comparison to normative data the Physical Component Summary score in the SF-36 instrument showed a return to normal levels at 12 months in both groups. In EuroQol-5D both groups reported full recovery after 6 months in all dimensions except in the dimension anxiety/depression. The recovery in this dimensions commenced between 6 and 12 months.

5 DISCUSSION

This thesis addresses the surgical treatment for perforated diverticulitis and discusses and a new and minimally invasive technique. Our randomised trial DILALA found a statistically significantly reduced risk of re-operations, shorter operating time and time in the recovery unit and shorter hospital stay. These results contribute to a future meta-analysis of all trials and scientific evidence and may help establish if there is sufficient evidence for a paradigm shift to laparoscopic lavage.

Considering that in Paper I (section 4.1) 44% of patients were re-operated, the permanent stoma rate was 40% and the mean length of hospital stay was 17 days, it would reasonable to say that a treatment reducing the percentage of re-operated patients, complications and length of stay would be beneficial for both patient and health care providers.

Laparoscopic lavage reportedly has the potential to reduce morbidity and mortality, but the evidence has been insufficient due to the lack of results from randomised controlled trials[42]. It is therefore important to evaluate whether laparoscopic lavage is a safe method and if it can be used as the recommended treatment for perforated diverticulitis.

When Paper III was published there were no results from other randomised trials, but in May 2015 Vennix et al published the results from a randomised controlled trial (the Ladies trial[19]) comparing laparoscopic lavage to Hartmann's procedure and primary resection with anastomosis. This trial consisted of two groups termed DIVA and LOLA, where LOLA[24] compared laparoscopic lavage with open surgery. The primary outcome measure was a composite endpoint including major morbidity and mortality within 12 months. The trial included 90 randomised patients but was then terminated during the interim analysis due to an increase in adverse events in the laparoscopic group. No statically significant difference between the two modalities could be detected in the composite primary endpoint.

In October 2015 Schultz et al presented their results from the randomised controlled SCANDIV-trial[25]. This trial also compared the outcome of laparoscopic lavage and Hartmann's procedure for perforated diverticulitis with purulent peritonitis. The primary endpoint was patients with severe complications (Clavien-Dindo >IIIa) within 90 days. This trial analysed 144 patients, and found no significant results for the primary endpoint.

In contrast to earlier studies[42] the outcomes of the two studies did not find laparoscopic lavage to be superior to resection. There are however fundamental differences in LOLA and SCANDIV compared to the DILALA-trial.

One factor that contributes to the divergent results is how LOLA and SCANDIV registered re-operations. The LOLA-trial did not consider an elective stoma reversal as a re-operation, but did for elective sigmoid resection. In the SCANDIV-trial re-operations and complications were only registered up until 90 days making the stoma reversal procedure a non-issue. They did, however include elective sigmoid resection due to cancer as a re-operation, as did we.

Another factor is that the LOLA trial regarded percutaneous drainage of an abscess as a re-operation. In the DILALA-trial this was classified as Clavien-Dindo IIIa and not considered a re-operation. It is debateable whether this should be considered as a re-operation or not, but it is our opinion that an ultrasonic guided percutaneous drainage requiring local anaesthesia performed by a radiologist is not an operation. We also suggest that most patients having had major surgery under general anaesthesia do not consider percutaneous drainage as a full-scale operation.

Originally, Hartmann's procedure was a one-stage operation for recto-sigmoid cancer resulting in a permanent stoma[43]. Today most surgeons consider the restoration of bowel continuity to be part of the treatment plan provided the patient is willing and fit for surgery at later stage.

Because there is no resection performed during laparoscopic lavage there is a risk that a sigmoid cancer can be missed during the initial acute procedure, but found later during a colonoscopy follow-up, which would result in a subsequent resection. Therefore all additional operations, which are a consequence of the treatment modality chosen, must be considered a re-operation.

In the DILALA-trial we decided to include all re-operations such as stoma reversal, wound dehiscence, stoma repair, open drainage of abscess and resection. We also argue that patients consider both sigmoid resection due to cancer and stoma reversal due to choosing Hartmann's procedure as full-scale operations.

It is possible that the differences between DILALA, SCANDIV and LOLA lie in the definition of what is regarded as a re-operation. In my opinion, it illustrates that the result is a consequence of the questions asked.

5.1 The Quality of Life assessment

Both groups reported full recovery after 6 months in the EuroQol-5D dimensions of mobility, self-care, usual activities, and pain/discomfort, whereas recovery in the dimension anxiety/depression commenced between 6 and 12 months. This finding has not been addressed and focus on mental health after 6 months could be beneficial for the patient. This, however, needs to be studied further since the DILALA-trial was not primarily designed for assessing quality of life.

5.2 If I were to do it differently

The structure of my doctoral thesis shows one way of how to obtain results by using data from a retrospective material and thereafter construct a clinical randomised trial. There are of course elements that in retrospect could have been done differently.

Ascertaining significant differences in health-related quality of life is a difficult undertaking. It becomes even harder to detect differences when quality of life is a secondary endpoint. Ideally an independent study with quality of life as a primary endpoint should have been conducted to maximise the opportunity to detect significant differences. It is also the issue of the time points selected for the questionnaires. For logistical reasons the time points selected was at discharge 6 months and 12 months. This was perhaps a too wide period of time between follow-ups. If the patient compared their situation at discharge and 4-6 weeks after the emergency operation the difference may have been more prominent.

Another noteworthy experience is the logistic difficulties of working with centres without a designated research administrator. A randomised study requires a level of accuracy, which is time-consuming. Without a person with dedicated time for tasks like collecting clinical reference forms, sending them to the coordinating centre and keeping up the screening log there is a risk of losing important data. In the DILALA study research personnel from the coordinating centre regularly visited participating hospitals to ensure no documentation was neglected, but in future studies it would be preferable

to also have research personnel at each centre dedicated for these assignments.

5.3 Clinical implications

The future of laparoscopic lavage as the gold standard treatment for perforated diverticulitis with purulent peritonitis is still uncertain.

While SCANDIV and LOLA did not demonstrate any significant differences between lavage and Hartmann with regard to re-operations, the DILALA-trial reported several significant advantages when using laparoscopic lavage. The pending results from the randomised controlled trial LapLAND[21] will play a crucial role in a potential paradigm shift.

6 CONCLUSION

- Patients operated due to perforated diverticulitis have high morbidity, considerable mortality and a substantial risk of re-operation.
- Forty per cent of patients operated with Hartmann's procedure at Sahlgrenska University Hospital 2003-2008 ended up with a permanent stoma.
- Laparoscopic lavage reduced the risk for a re-operation, operating time and length of hospital stay compared to Hartmann's procedure.
- No significant differences in adverse events between laparoscopic lavage and Hartmann's procedure were seen.

7 FUTURE PERSPECTIVES

7.1 Laparoscopic lavage for other conditions with purulent peritonitis?

Our study cannot explain the beneficial mechanisms of laparoscopic lavage.

A possible explanation for the potential benefits of laparoscopic lavage is that with irrigation and drainage the pus is removed, which provides an improved environment for potential self-healing, and by not resecting the colon the intraabdominal dissection is reduced which causes less tissue damage.

There are also indications that the effect of the carbon dioxide used for the peritoneal inflation may have a beneficial effect on the inflammatory response and immune system[44].

But this is speculation and more research is needed in order to better understand the mechanisms of laparoscopic lavage. It could be interesting to explore if the possible benefits of laparoscopic lavage may be potentially beneficial to other diagnosis such as perforated appendicitis with purulent peritonitis or purulent gynaecological infections.

7.2 Laparoscopic lavage as the gold standard?

When implementing new treatment modalities the evidence for change needs to be sufficient to assure patient safety. The outcome of case series, prospective- and retrospective studies should be regarded with caution before implementing a new treatment. Prior to LOLA and SCANDIV there were no studies indicating increased morbidity or mortality for laparoscopic lavage. However, the negative outcome of these two randomised controlled studies should be considered carefully, because the primary endpoint did not show any significant difference between the two modalities.

In summary, the scientific evidence for laparoscopic lavage is still limited but our results indicate that laparoscopic lavage is superior to Hartmann's procedure when treating perforated diverticulitis with purulent peritonitis.

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APPENDIX

EuroQol-5D

The EuroQol-5D is a generic instrument in which the patient answers multiple-choice questions ('no problems', 'low levels of problems' and 'severe problems'). The questions are organised into five dimensions and reflect the respondent's situation on the day of completion. The dimensions are mobility, self-care, usual activities, pain/comfort and anxiety/depression. A visual analogue scale is part of the evaluation. This is graded from 'worst imaginable health state' (0) to 'best imaginable health state' (100). The answers reflect the current health status on the day of the follow-up. The EuroQol-5D is a well-established and extensively used instrument of measuring quality of life in many different patient populations[45].

Short-Form 36 Health Survey

The other instrument used in the DILALA-trial was the Short-Form 36 Health Survey (SF-36). SF-36 is like EuroQol-5D a generic instrument. It reflects a 14-day recall period and consists of eight different sections (vitality, physical function, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning and mental health). These sections can be summarised in two scores (Physical Component Summary score and Mental Component Summary score) reflecting the general mental and physical health of the cohort.

EORTC QLQ-C30 and QLQ-CR38

These two instruments are designed specifically for patients with cancer but some of the questions are relevant to patients undergoing operations for acute perforated diverticulitis. Several questions were excluded as they were not applicable to diverticulitis patients and the selected questions primarily aim to address stoma related problems, urinary problems, alterations in bowel habits and health economy issues. These instruments have not yet been analysed and are therefore not discussed in this thesis.