National Institute for Health and Care Excellence

Final

Diverticular disease: diagnosis and management

[O] Evidence review for laparoscopic lavage for the management of bowel perforations

NICE guideline NG147

Intervention evidence review

November 2019

Final

This evidence review was developed by the National Guideline Centre

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Contents

1 Laparoscopic lavage versus resectional surgery

1.1 Review question: What is the clinical and cost effectiveness of laparoscopic lavage versus resectional surgery for the management of bowel perforations?

1.2 Introduction

Perforated diverticular disease is most commonly treated by resection of the affected segment of bowel and formation of an end stoma (Hartmann's procedure) or primary resection and anastomosis with or without a diverting stoma. These operations are associated with a high morbidity and mortality and often leave patients with a permanent stoma. Due to the high morbidity and mortality there has been a drive to pursue less invasive surgical procedures. One such procedure is the use of laparoscopic lavage for patients presenting with purulent peritonitis secondary to diverticular perforation. This review aimed to provide evidence of the clinical and cost effectiveness of this approach compared to resectional surgery.

1.3 PICO table

For full details see the review protocol in appendix A.

Table 1: PICO characteristics of review question

Population	Adults aged 18 years and over with diverticular bowel perforations
Intervention	Laparoscopic lavage
Comparison	Resectional surgery

Outcomes	**Critical outcomes**:
	• Quality of life
	• Mortality
	• Morbidity
	• Progression of disease
	• Complications:
	  ○ infections
	  ○ abscesses
	  ○ perforation
	  ○ fistula
	  ○ stricture
	  ○ Haemorrhage
	• Re-hospitalisation
	• Need for further intervention (e.g. surgery, percutaneous drainage)
	• Anastomotic leak rate
	• Stoma formation

Study design	Randomised controlled trials (RCTs), systematic reviews of RCTs. If no sufficient RCT evidence is available, search for observational studies.

1.4 Clinical evidence

1.4.1 Included studies

Three randomised controlled trials were included in this review, reported across ten studies;[6, 20, 26, 43, 44, 48-50, 53, 54] these are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summary below (Table 3).

See also the study selection flow chart in appendix C, study evidence tables in appendix D, forest plots in appendix E and GRADE tables in appendix F.

1.4.2 Excluded studies

Since there was sufficient RCT evidence, observational studies were not considered for this review.

See the excluded studies list in appendix I.

1.4.3 Summary of clinical studies included in the evidence review

Table 2: Summary of studies included in the evidence review

Trial; Study	Intervention and comparison	Population	Outcomes	Comments/concomitant treatment
DILALA trial; Angenete 2016[6], Gehram 2016[20], Thornell 2016[49] Thornell 2011[50] Kohl 2018[26] 24 months follow up	Laparoscopic lavage Open Hartmann procedure	Inclusion of patients was based on radiologic examination of the abdomen showing intra-abdominal fluid or gas and a decision to perform surgery followed by the patient's informed consent. Included population had Hinchey grade III diverticulitis	Quality of life Mortality Morbidity (adverse events) Complications: abscess Rehospitalisation Further intervention (surgery) Stoma formation	A passive drain was placed in the pelvis in all patients and left in place for at least 24 hours. Both groups were treated postoperatively according to local routines regarding antibiotic treatment, thrombosis prophylaxis and return to oral feeding.
LADIES trial; Vennix 2015[53], Vennix 2017[54], Swank 2010[48] 12 months follow up	Laparoscopic lavage Resectional surgery; Hartmann procedure or sigmoidectomy with primary anastomosis.	People with perforated diverticulitis based on radiological examination by radiography or a CT scan showing diffuse-free intraperitoneal air or fluid Included population had Hinchey grade III diverticulitis	Quality of life Mortality Morbidity Disease progression (recurrence) Complications: abscess Complications: wound infection Further intervention (surgery) Stoma formation	All patients given antibiotics for 7 days post-surgery. 4-6 weeks after surgery, sigmoidoscopy was done to exclude malignancy. Resection: Patients were offered stoma reversal if they were fit enough for another surgical procedure.
SCANDIV trial; Schulz 2015[44], Schulz 2017[43] 12 months follow up	Laparoscopic lavage Resectional surgery; laparoscopic or open resection, Hartmann procedure or anastomosis.	Inclusion of patients was based on diagnostic imaging results (via an abdominal CT scan) showing free air and findings compatible with perforated diverticulitis (usually including colonic wall	Hinchey grade III and IV: Quality of life Hinchey grade III: Mortality Morbidity (severe complications) Disease progression	All patients were administered intravenous antibiotics, according to local practices, after a diagnosis of peritonitis was established. In both groups, the time to drain removal was determined by the surgeon.

Trial; Study	Intervention and comparison	Population	Outcomes	Comments/concomitant treatment
		thickening and pericolic inflammation). Majority of the included population had either Hinchey grade III or Hinchey grade IV diverticulitis.	(recurrence) Complications: abscess Complications: infection Further intervention (surgery) Rehospitalisation Stoma formation	Resection group: intervention was determined by surgeon.

See appendix D for full evidence tables.

1.4.4 Quality assessment of clinical studies included in the evidence review

Table 3: Clinical evidence summary: laparoscopic lavage versus resectional surgery

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Lavage versus resectional surgery (95% CI)
Quality of life-Cleveland quality of life score 12 months Scale from: 0 to 1.	119 (1 study) 12 months	⊕⊕⊕⊖ MODERATE[a] due to risk of bias			The mean quality of life-cleveland quality of life score 12 months in the intervention groups was 0.02 lower (0.03 to 0.01 lower)
Quality of life- EQ5D 3L VAS 6 months Scale from: 0 to 100.	64 (1 study) 6 months	⊕⊖⊖⊖ VERY LOW[a,b] due to risk of bias, inconsistency, imprecision			The mean quality of life- eq5d 3l vas 6 months in the intervention groups was 1.2 higher (6.56 lower to 8.96 higher)
Quality of life- SF36 6 months - Physical Scale from: 0 to 100.	64 (1 study) 6 months	⊕⊕⊖⊖ LOW[a,c] due to risk of bias, imprecision			The mean quality of life- sf36 6 months - physical in the intervention groups was 1.5 higher (2.4 lower to 5.4 higher)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Lavage versus resectional surgery (95% CI)
Quality of life- SF36 6 months - Mental Scale from: 0 to 100.	64 (1 study) 6 months	⨁⨁⊖⊖ LOW[a,c] due to risk of bias, imprecision			The mean quality of life- sf36 6 months - mental in the intervention groups was 0.2 higher (4.98 lower to 5.38 higher)
Mortality at end of follow-up	315 (3 studies)	⨁⊖⊖⊖ VERY LOW[a,c] due to risk of bias, imprecision	RR 0.84 (0.47 to 1.51)	Moderate	
				119 per 1000	19 fewer per 1000 (from 63 fewer to 61 more)
Morbidity/adverse events 12 months	343 (3 studies) 12 months	⨁⨁⨁⊖ MODERATE[c] due to imprecision	RR 1.31 (1.04 to 1.67)	Moderate	
				476 per 1000	148 more per 1000 (from 19 more to 319 more)
Progression of disease: recurrent diverticulitis 12 months	232 (2 studies) 12 months	⨁⨁⨁⨁ HIGH	RR 8.36 (1.99 to 35.18)	Moderate	
				19 per 1000	140 more per 1000 (from 19 more to 649 more)
Complication: Abscess 12 months	315 (3 studies) 12 months	⨁⨁⊖⊖ LOW[a,c] due to risk of bias, imprecision	RR 1.75 (1 to 3.07)	Moderate	
				48 per 1000	36 more per 1000 (from 0 more to 99 more)
Complication: infections 12 months	232 (2 studies) 12 months	⨁⊖⊖⊖ VERY LOW[a,c,d] due to risk of bias, inconsistency, imprecision	RR 0.55 (0.10 to 3.02)	Moderate	
				257 per 1000	116 fewer per 1000 (from 231 fewer to 519 more)
Hospital readmission (un/planned) at end of follow-up	171 (2 studies)	⨁⊖⊖⊖ VERY LOW[c,e] due to inconsistency, imprecision	RR 1.1 (0.76 to 1.59)	Moderate	
				452 per 1000	45 more per 1000 (from 108 fewer to 267 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Lavage versus resectional surgery (95% CI)
Unplanned hospital readmissions	227 (2 studies) 12 months	⊕⊕⊖⊖ LOW[a,c] due to risk of bias, imprecision	OR 2.35 (1.23 to 4.51)	Moderate	
				114 per 1000	118 more per 1000 (from 23 more to 253 more)
Reoperations at end of follow-up	315 (3 studies) 12-24months	⊕⊕⊕⊖ MODERATE[c] due to imprecision	RR 0.74 (0.57 to 0.95)	Moderate	
				625 per 1000	162 fewer per 1000 (from 31 fewer to 256 fewer)
Stoma formation up to 24 months (excluding formation as part of the index operation) [f]	83 (1 study) 24 months	⊕⊕⊖⊖ LOW[c] due to imprecision	RR 1.4 (0.25 to 7.92)	Moderate	
				25 per 1000	10 more per 1000 (from 19 fewer to 173 more)
Stoma at end-of follow up	288 (3 studies)	⊕⊕⊕⊕ HIGH	RR 0.32 (0.19 to 0.54)	Moderate	
				306 per 1000	208 fewer per 1000 (from 141 fewer to 248 fewer)

a Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

b Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs. MID is 0.03 for EQ5D.

c Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.

d The point estimate varies widely across studies, unexplained by subgroup analysis.

e Downgraded by 1 or 2 increments because the point estimate varies widely across studies.

f These values represent the number of stomas formed during the 24 month period, not the total number of the stomas present at the end of the 24 month period and it also doesn't take into account the number of stoma reversals during this period.

See appendix F for full GRADE tables.

1.5 Economic evidence

1.5.1 Included studies

Two health economic studies were identified with the relevant comparison and have been included in this review. [20, 54] These are summarised in the health economic evidence profile below (Table 4) and the health economic evidence tables in appendix H.

1.5.2 Excluded studies

No health economic studies that were relevant to this question were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in appendix G.

1.5.3 Summary of studies included in the economic evidence review

Table 4: Health economic evidence profile: laparoscopic lavage versus resectional surgery

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Gehrman, 2016[20] (Sweden)	Partially applicable [(a)]	Potentially serious limitations[(b)]	Within-trial cost-consequences analysis of DILALA RCT with post-trial extrapolation. Trial compared laparoscopic lavage with Hartmann's procedure only.	Laparoscopic lavage saves £18,871[(e)]	**EQ-5D VAS, 1 year:** 5 lower **Mortality, 1 year:** RR: 0.93 [95% CI: 0.33 to 2.65] **Morbidity, 1 year:** RR: 1.30 [95% CI: 0.89 to 1.90]	n/a	One-way sensitivity analysis was performed on the costs of (varied by 30%) to assess the impact on the results. Robustness was demonstrated through varying the costs for each variable for base case B (lifetime time horizon).
Vennix, 2017 [54] (The Netherlands)	Partially applicable [(c)]	Potentially serious limitations[(d)]	Within-trial analysis of LADIES RCT with post-trial extrapolation to lifetime time horizon for costs.	Laparoscopic lavage saves £8,417[(f)]	**QALYs (mean per patient), 1 year:** 0.032 QALYs lost (95% BCaCI: 0.147 lost to 0.081 gained) **Mortality, 1 year:** RR: 0.61 [95% CI: 0.18 to 2.01] **Morbidity, 1 year:** RR: 1.37 [95% CI: 0.94 to 2.00]	**1 year:** £166,811 per QALY gained (dominant to £1,574,491) £93,618 per poor outcome averted (major morbidity and mortality at 1 year)	Probability Resection is cost effective (€30,000 per QALY gained threshold): 14.7%

Abbreviations: n/a: not applicable; QALY: quality-adjusted life years; RCT: randomised controlled trial

(a) Within-trial analysis of DILALA RCT with post-trial extrapolation. Sweden, healthcare sector perspective.

(b) Some unit costs obtained by interview with an economist at Sahlgrenska University Hospital. Time in intensive care unit was excluded from the cost analysis because it was deemed unrelated to the underlying surgical technique. Discounting of costs and outcomes not reported. Quality of life assessment did not include pre-operative baseline questionnaires due to severity of disease on admission; a baseline evaluation at discharge was recorded.

(c) Within-trial analysis of LADIES RCT with post-trial extrapolation for costs only. The Netherlands, societal perspective

(d) There was a relatively high proportion of patients having primary anastomosis (50%). Patient's travel expenses and informal home care included, differing from NICE Reference Case. For the within-trial portion of the analysis, quality of life reported at 6 months was extrapolated to 12 months. Discounting not reported. Quality of life with EQ-5D incorrectly calculated in accompanying trial publication as an average of scores across 3 dimensions, reported as a 'health state'. [53]Unclear whether EQ-5D 'health state' data or EQ-5D VAS data were used in the calculation of QALYs at 1 year.

(e) Converted using 2016 purchasing power parities[35]

(f) *Converted using 2012 purchasing power parities[35]*

1.5.4 Unit costs

The unit costs below were presented to the committee, to aid consideration of cost effectiveness.

Table 5: UK costs of procedures

Procedure	Currency Description	Unit Cost	Average Length of Stay	Source
Introduction of substance into peritoneal cavity	FF52 Intermediate Therapeutic General Abdominal Procedures, 19 years and over, inclusive of non-elective short stay and non-elective long stay with excess bed days, weighted for complications and co morbidities for HRG codes: FF52A, FF52B and FF52C; as recorded for Non-Elective Inpatients)	£3,891	5.15 days	NHS Reference Costs 2016-2017
Sigmoid colectomy and anastomosis	FF33 Distal Colon Procedures, 19 years and over, inclusive of non-elective short stay and non-elective long stay with excess bed days, weighted for complications and co morbidities for HRG codes: FF33A and FF33B; as recorded for Non-Elective Inpatients	£7,091	9.0 days	NHS Reference Costs 2016-2017
Sigmoid colectomy and ileostomy HFQ Or Sigmoid colectomy and exteriorisation of bowel NEC	FF31 Complex Large Intestine Procedures, 19 years and over, inclusive of non-elective short stay and non-elective long stay with excess bed days, weighted for complications and co morbidities for HRG codes: FF31A, FF31B, FF31C and FF31D; as recorded for Non-Elective Inpatients	£8,312	11.0 days	NHS Reference Costs 2016-2017

1.5.5 Health economic modelling

An original cost-utility analysis was developed using a decision tree for the first year. The full report can be found in a separate document - Appendix 2.

A Markov model was used to estimate the longer term costs and benefits up to 10 years. The following sources were used to populate the model:

- Probabilities of events in year one were pooled from the three included randomised trials of laparoscopic lavage versus resection for perforated diverticulitis. [53 44 49]
- Survival and mortality data came from HES-ONS[34] linked data and a cohort study of 340 patients with perforated diverticulitis[56]
- Recurrence rates were taken from a study of 3222 patients admitted with acute diverticulitis.[10]
- Unit costs were taken from the NHS Reference costs.[17]
- Utility data came from a cohort of 121 patients with perforated diverticulitis. [55]

Table 6: Base case results - cost effectiveness

	Mean Cost (discounted)	Mean QALYs (discounted)	Cost effectiveness
Year 1			
Laparoscopic lavage	7,500	0.67	
Resection	13,394	0.67	
Lavage vs Resection	- 5,894	0.01	Lavage dominates Resection
All years (1-10)			
Laparoscopic lavage	10,518	4.55	
Resection	18,586	4.51	
Lavage vs Resection	- 8,068	0.04	Lavage dominates Resection

As can be seen in Table 6, laparoscopic lavage was both cost saving and had QALY gains compared with resection. These gains were even larger after 10 years than at one year.

A number of sensitivity analyses were conducted and the incremental results varied considerably. The incremental cost of laparoscopic lavage ranged from a saving of £12,000 per patient to a loss of £3,000. Incremental QALYs ranged from a loss of 0.5 to a gain of 0.2.

Laparoscopic lavage was the lowest cost strategy for all except one sensitivity analysis. That was when it was assumed that all patients in the resection arm had primary anastomosis without diverting ileostomy. In this scenario, Resection dominated Lavage. This is due to the lower mortality assumed after this procedure, zero reoperation rate and zero long term costs assumed. In a threshold analysis we found that lavage was cost saving compared with resection unless only 4.5% or fewer patients in the resection arm had Hartmann's procedure (rather than primary anastomosis).

There were a few scenarios where resection was more costly than lavage but had more QALYs:

- When year 1 probabilities were taken only from the SCANDIV trial.
- When it was assumed that all patients in the resection arm had primary anastomosis without diverting ileostomy
- When the one-year resection rate after lavage increased to 50%.
- When it was assumed that there is no difference in mortality at one year
- When the resection rate after lavage was high
- When a quality of life decrement was applied to lavage.

But in these scenarios the increased QALYs associated with resection were not large enough to justify the extra cost. That is, they cost more than £20,000 per QALY gained.

1.6 Evidence statements

1.6.1 Clinical evidence statements

There was no evidence of a clinical difference between lavage and resection in quality of life at 6 (1 study, n=64, very low to low quality on three separate scales) and 12 (1 study, n=119, moderate quality) months. Similarly, 3 RCTs (n=315, very low quality) indicated uncertainty around the effect estimate for mortality at 12-24 months follow-up, meaning no clinical difference could be detected between the two interventions. In addition, uncertainty around

the effect estimate was also observed by 2 studies (n=232, very low quality) reporting on complications (infections) at 12 months, with no difference between lavage and resection being observed.

Concerning morbidity/adverse events (n=343, moderate quality) and complications (abscess; n=315, low quality), all 3 studies reported on this outcome at 12 months follow-up and indicated a clinical benefit of resection over lavage. In addition, 2 studies (n=232, high quality) demonstrated a clinical benefit of resection in terms of progression of disease (recurrence of diverticulitis).

In terms of readmissions, 2 studies (n=171, very low quality) reported on planned and unplanned rehospitalisations combined at end of follow-up (12-24 months) and 2 studies (n=227, low quality) reported on unplanned readmissions alone at 12 months follow-up; uncertainty in the effect estimate for planned and unplanned rehospitalisations combined meant that no clinical difference could be identified for this outcome, while the results for unplanned readmissions alone indicated a clinical benefit of resection over lavage. By contrast, the results of 3 studies (n=315, moderate quality) for reoperations (planned and unplanned) at 12-24 months follow-up indicated a clinical benefit of lavage compared with resection.

There was evidence from 3 studies (n=288, high quality) for a clinical benefit of lavage over resection in terms of stoma at end of follow-up (12-24 months). However, no clinical difference could be detected between lavage and resection in 1 study (n=83, low quality) reporting on Stoma formation up to 24 months (excluding formation as part of the index operation).

1.6.2 Health economic evidence statements

- One published cost-utility analysis found that resection was not cost effective compared with laparoscopic lavage for patients with perforated diverticulitis (£166,000 per QALY gained). This was rated as partially applicable with potentially serious limitations.
- One published cost analysis found that laparoscopic lavage was cost saving compared with Hartmann's procedure for patients with perforated diverticulitis (£19,000 saved per patient). This was rated as partially applicable with potentially serious limitations.
- One original cost-utility analysis found that laparoscopic lavage was cost saving compared with resection for patients with perforated diverticulitis (£8000 saved per patient). This was rated as partially applicable with potentially serious limitations.

1.7 The committee's discussion of the evidence

1.7.1 Interpreting the evidence

1.7.1.1 The outcomes that matter most

The guideline committee agreed that for this review quality of life, mortality, morbidity, progression of disease, complications (infections, abscesses, perforation, fistula, stricture, haemorrhage), re-hospitalisation, need for further intervention (for example surgery, percutaneous drainage), anastomotic leak rate and stoma formation were considered critical outcomes. No important outcomes were specified for this review.

In this review, no clinical evidence was identified for the following critical outcomes; complications (perforation, fistula, stricture and haemorrhage) and anastomotic leak rate.

The committee noted that most of the outcomes presented were at a follow-up of 12 months and that outcomes further down the line, for example at 2-3 years post-resection or lavage, would be more useful which was only reported in one study. They specifically mentioned that

information concerning the quality of life and need for further surgery at a longer follow-up would be more informative as, in terms of need for further surgery, the committee were interested in establishing the proportion of patients originally undergoing lavage that would eventually require resection at time-points longer than 12 months post-lavage.

1.7.1.2 The quality of the evidence

All of the clinical evidence presented in this review was from RCTs. The quality of this evidence ranged from very low to high for different outcomes. Where the quality was downgraded, this was predominantly due to risk of bias and/or imprecision, with incomplete outcome data being the major reason for downgrading due to risk of bias.

1.7.1.3 Benefits and harms

The review of the clinical evidence demonstrated that for most outcomes; quality of life, and mortality, complications (infection) and Stoma formation (excluding formation as part of the index operation), there was either no clinical difference between resection and lavage or there was too much uncertainty in the effect estimate to favour one over the other. Despite there being no evidence of differences between the interventions for these outcomes, the committee highlighted the small number of participants included in each trial and that this should be interpreted with caution.

Outcomes where there was evidence for a clinical benefit of resection included morbidity/adverse events, progression of disease (recurrent diverticulitis), abscess and unplanned hospital readmissions. However, the committee noted that a reduced recurrence of diverticulitis in the resection group compared with the lavage group was to be expected due to the fact that the diseased bowel has been removed in the resection group and therefore recurrence is unlikely.

Outcomes where there was evidence for a clinical benefit of lavage included hospital readmission, reoperation and stoma. However, the committee noted that the hospital readmission and reoperation outcomes included both planned and unplanned admissions/operations, meaning stoma reversal operations were included for the resection group and this may have affected the result for these outcomes.

All of the reported outcomes were considered critical by the committee. As there was no evidence of a difference between the two interventions for the majority of outcomes, the committee agreed that both resectional surgery and lavage should be offered to patients presenting with diverticular perforation. Although a larger number of outcomes suggested a clinical benefit of resection compared with lavage, the committee noted that the clinical evidence did not suggest any difference in mortality risk compared with resection. In addition, the committee placed emphasis on avoiding stoma formation in patients where possible due to the low reversal rate of stomas and ongoing cost of stoma management, and possibly reduced quality of life with stoma. They agreed that the increased risk of abscess formation and recurrence of diverticulitis would be at least partially offset by the benefits of avoiding stoma.

The committee noted that there is currently no guidance concerning which patients to perform lavage on, a comment that was made by the three included trials in this review. For this reason, they agreed that both should be offered and the choice could be based on patient and/or surgeon preference. However, the committee stressed that if faecal peritonitis is observed during lavage then the operating surgeon should proceed to resection due to the more serious nature of this condition compared with purulent peritonitis.

Overall, the committee agreed that there was insufficient strong clinical evidence to support not offering lavage as an alternative to resection in patients with diverticular perforation. The committee concluded that lavage and resection should be offered to patients with

generalised peritonitis and diverticular perforation, unless faecal peritonitis was identified, in which case resection should be performed.

1.7.2 Cost effectiveness and resource use

Two published economic evaluations (a cost-utility analysis and a cost-consequences analysis) were included, each based on one of the included randomised trials. An original cost-utility analysis was developed to incorporate both these trials and also SCANDIV.

Laparoscopic lavage is a faster, lower cost procedure with a shorter length of hospital stay than resection. There is a trend towards improved survival and substantially fewer patients are left with a long-term stoma but there is an increase in morbidity.

All three economic evaluations found lavage to be cost saving, since there were fewer re-operations and fewer people with long-term stoma. The published cost-utility analysis found resection to have slightly more QALYs but not enough to achieve an acceptable level of cost effectiveness. The original economic evaluation found lavage to be dominant in the base case analysis. It had fewer QALYs than resection in a number of sensitivity analyses. There was only one sensitivity analysis that favoured resection in terms of cost effectiveness: laparoscopic lavage was dominated by resection if it was assumed that 94.5% or more resections are primary anastomoses. The proportion of resections that are primary anastomoses nationally is not known but the committee believe that it is much lower than this.

It should not be concluded that primary anastomosis is more cost effective than both laparoscopic lavage and Hartmann's procedure for the following reasons:

- The evidence comparing these two procedures is highly uncertain because studies have failed to control for confounding adequately (see Chapter M).
- The committee's experience suggests that various patient characteristics might favour one type of resection over another. For example, in the emergency setting frail patients with multiple medical problems may benefit from a Hartmann's procedure as this removes the risk of a subsequent anastomotic leak. For these reasons and because of the design of the SCANDIV trial, a blended comparator of different types of resection was chosen.
- The assumption that there would be no recurrence and no further procedures in the post-anastomosis state was an assumption that was made to simplify the model and with the deliberate intention of biasing the model against lavage. However, it has the unintended consequence of making anastomosis appear more cost effective than Hartmann's procedure.

Overall, there is a lot of uncertainty because the three trials are relatively small and heterogeneous and there is little long-term evidence for lavage, especially in terms of survival and quality of life.

This recommendation is likely to lead to cost savings to the NHS, since laparoscopic lavage is not commonly conducted in the UK and therefore its more widespread use should lead to less people requiring long-term stoma care and possibly fewer total operations (elective and emergency combined).

On the basis of the published and original economic evidence supporting laparoscopic lavage, the committee decided to offer lavage as an alternative to resection. Given the uncertainty in the evidence base, it was decided that there is still a role for resection and that patient choice should be the deciding factor.

1.7.3 Other factors the committee took into account

The formation of a stoma may be a deterrent to surgery for some people with perforations as a result of the potential impact a stoma could have on their quality of life. However others would rather have a stoma and be alleviated from their pain and its resulting lowered quality of life.

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Appendices

Appendix A: Review protocols

Table 7: Review protocol: laparoscopic lavage versus resectional surgery

Field	Content
Review question	What is the clinical and cost effectiveness of laparoscopic lavage versus resectional surgery for the management of bowel perforations?
Type of review question	intervention review A review of health economic evidence related to the same review question was conducted in parallel with this review. For details see the health economic review protocol for this NICE guideline.
Objective of the review	To determine whether laparoscopic lavage is more clinically and cost effective than resectional surgery for the management of bowel perforations
Eligibility criteria – population / disease / condition / issue / domain	Adults 18 years and over with diverticular bowel perforations
Eligibility criteria – intervention(s) / exposure(s) / prognostic factor(s)	Laparoscopic lavage
Eligibility criteria – comparator(s) / control or reference (gold) standard	Resectional surgery

Outcomes and prioritisation	Critical outcomes:
	• Quality of life
	• Mortality
	• Morbidity
	• Progression of disease
	• Complications:
	  ○ infections
	  ○ abscesses
	  ○ perforation
	  ○ fistula
	  ○ stricture
	  ○ Haemorrhage
	• Re-hospitalisation
	• Need for further intervention (e.g. surgery, percutaneous drainage)
	• Anastomotic leak rate
	• Stoma formation

Eligibility criteria – study design	Randomised controlled trials (RCTs), systematic reviews of RCTs. If no sufficient RCT evidence is available, search for observational studies
Other inclusion exclusion criteria	Exclusions: • Children and young people aged 17 years and younger
Proposed sensitivity / subgroup analysis, or	Subgroups:

meta-regression	• people of Asian family origin as they are known to develop right-sided diverticula • Immunocompromised population • Aged <50, ≥50 years
Selection process – duplicate screening / selection / analysis	Studies are sifted by title and abstract. Potentially significant publications obtained in full text are then assessed against the inclusion criteria specified in this protocol.
Data management (software)	• Pairwise meta-analyses performed using Cochrane Review Manager (RevMan5). • GRADEpro used to assess the quality of evidence for each outcome • Bibliographies, citations and study sifting managed using EndNote • Data extractions performed using EviBase, a platform designed and maintained by the National Guideline Centre (NGC)
Information sources – databases and dates	Medline, Embase, The Cochrane Library
Identify if an update	Not applicable
Author contacts	https://www.nice.org.uk/guidance/conditions-and-diseases/digestive-tract-conditions/diverticular-disease
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual.
Search strategy – for one database	For details please see appendix B
Data collection process – forms / duplicate	A standardised evidence table format will be used, and published as appendix D of the evidence report.
Data items – define all variables to be collected	For details please see evidence tables in Appendix D (clinical evidence tables) or G (health economic evidence tables).
Methods for assessing bias at outcome / study level	Standard study checklists were used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
Criteria for quantitative synthesis	For details please see section 6.4 of Developing NICE guidelines: the manual.
Methods for quantitative analysis – combining studies and exploring (in)consistency	For details please see the separate Methods report (Chapter R) for this guideline.
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual.
Confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual.
Rationale / context – what is known	For details please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the evidence review. The committee was convened by the National Guideline Centre (NGC) and chaired by James Dalrymple in line with section 3 of Developing NICE guidelines: the manual. Staff from NGC undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the evidence review in collaboration with

	the committee. For details please see Developing NICE guidelines: the manual.
Sources of funding / support	NGC is funded by NICE and hosted by the Royal College of Physicians.
Name of sponsor	NGC is funded by NICE and hosted by the Royal College of Physicians.
Roles of sponsor	NICE funds NGC to develop guidelines for those working in the NHS, public health and social care in England.
PROSPERO registration number	Not registered

Table 8: Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2002, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[32] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies

	excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2002 or later but that depend on unit costs and resource data entirely or predominantly from before 2002 will be rated as 'Not applicable'. • Studies published before 2002 will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B: Literature search strategies

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual 2014, updated 2017

For more detailed information, please see the Methodology Review.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 9: Database date parameters and filters used

base	s searched	ch filter used
ine (OVID)	– 13 November 2018	sions omised controlled trials matic review studies
ase (OVID)	– 13 November 2018	sions

base	s searched	ch filter used
		omised controlled trials matic review studies
Cochrane Library (Wiley)	rane Reviews to 2018 Issue 11 of 12 TRAL to 2018 Issue 11 of 12 E, and NHSEED to 2015 Issue 2 of 4 to 2016 Issue 2 of 4	

Table 10: Medline (Ovid) search terms

1.	diverticul*.mp.
2.	limit 1 to English language
3.	letter/
4.	editorial/
5.	news/
6.	exp historical article/
7.	Anecdotes as Topic/
8.	comment/
9.	case report/
10.	(letter or comment*).ti.
11.	or/3-10
12.	randomized controlled trial/ or random*.ti,ab.
13.	11 not 12
14.	animals/ not humans/
15.	exp Animals, Laboratory/
16.	exp Animal Experimentation/
17.	exp Models, Animal/
18.	exp Rodentia/
19.	(rat or rats or mouse or mice).ti.
20.	or/13-19
21.	2 not 20
22.	randomized controlled trial.pt.
23.	controlled clinical trial.pt.
24.	randomi#ed.ti,ab.
25.	placebo.ab.
26.	randomly.ti,ab.
27.	Clinical Trials as topic.sh.
28.	trial.ti.
29.	or/22-28
30.	Meta-Analysis/
31.	exp Meta-Analysis as Topic/
32.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
33.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
34.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
35.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
36.	(search* adj4 literature).ab.

37.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
38.	cochrane.jw.
39.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
40.	or/50-59
41.	21 and (29 or 40)

Table 11: Embase (Ovid) search terms

1.	diverticul*.mp.
2.	limit 1 to English language
3.	letter.pt. or letter/
4.	note.pt.
5.	editorial.pt.
6.	case report/ or case study/
7.	(letter or comment*).ti.
8.	or/3-7
9.	randomized controlled trial/ or random*.ti,ab.
10.	8 not 9
11.	animal/ not human/
12.	nonhuman/
13.	exp Animal Experiment/
14.	exp Experimental Animal/
15.	animal model/
16.	exp Rodent/
17.	(rat or rats or mouse or mice).ti.
18.	or/10-17
19.	2 not 18
20.	random*.ti,ab.
21.	factorial*.ti,ab.
22.	(crossover* or cross over*).ti,ab.
23.	((doubl* or singl*) adj blind*).ti,ab.
24.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
25.	crossover procedure/
26.	single blind procedure/
27.	randomized controlled trial/
28.	double blind procedure/
29.	or/20-28
30.	systematic review/
31.	meta-analysis/
32.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
33.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
34.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
35.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
36.	(search* adj4 literature).ab.

37.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
38.	cochrane.jw.
39.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
40.	or/30-39
41.	19 and (29 or 40)

Table 12: Cochrane Library (Wiley) search terms

#1.	diverticul*.mp.

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to Diverticular Disease population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA) with no date restrictions. NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional searches were run on Medline and Embase for health economics, economic modelling and quality of life studies.

Table 13: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	1946 – 13 November 2018	Exclusions Health economics studies Health economics modelling studies Quality of life studies
Embase	1974 – 13 November 2018	Exclusions Health economics studies Health economics modelling studies Quality of life studies
Centre for Research and Dissemination (CRD)	HTA - Inception – 13 November 2018 NHSEED - Inception to March 2015	None

Table 14: Medline (Ovid) search terms

1.	diverticul*.mp.
2.	limit 1 to English language
3.	letter/
4.	editorial/
5.	news/
6.	exp historical article/
7.	Anecdotes as Topic/
8.	comment/
9.	case report/
10.	(letter or comment*).ti.

11.	or/3-10
12.	randomized controlled trial/ or random*.ti,ab.
13.	11 not 12
14.	animals/ not humans/
15.	exp Animals, Laboratory/
16.	exp Animal Experimentation/
17.	exp Models, Animal/
18.	exp Rodentia/
19.	(rat or rats or mouse or mice).ti.
20.	or/13-19
21.	2 not 20
22.	Economics/
23.	Value of life/
24.	exp "Costs and Cost Analysis"/
25.	exp Economics, Hospital/
26.	exp Economics, Medical/
27.	Economics, Nursing/
28.	Economics, Pharmaceutical/
29.	exp "Fees and Charges"/
30.	exp Budgets/
31.	budget*.ti,ab.
32.	cost*.ti.
33.	(economic* or pharmaco?economic*).ti.
34.	(price* or pricing*).ti,ab.
35.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
36.	(financ* or fee or fees).ti,ab.
37.	(value adj2 (money or monetary)).ti,ab.
38.	or/22-37
39.	exp models, economic/
40.	*Models, Theoretical/
41.	markov chains/
42.	monte carlo method/
43.	exp Decision Theory/
44.	(markov* or monte carlo).ti,ab.
45.	econom* model*.ti,ab.
46.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
47.	Models, Organizational/
48.	*models, statistical/
49.	*logistic models/
50.	models, nursing/
51.	((organi?ation* or operation* or service* or concept*) adj3 (model* or map* or program* or simulation* or system* or analys*)).ti,ab.
52.	(econom* adj2 (theor* or system* or map* or evaluat*)).ti,ab.
53.	(SSM or SODA).ti,ab.
54.	(strateg* adj3 (option* or choice*) adj3 (analys* or decision*)).ti,ab.

55.	soft systems method*.ti,ab.
56.	(Meta-heuristic* or Metaheuristic*).ti,ab.
57.	(dynamic* adj2 (model* or system*)).ti,ab.
58.	(simulation adj3 (model* or discrete event* or agent)).ti,ab.
59.	(microsimulation* or "micro* simulation*").ti,ab.
60.	((flow or core) adj2 model*).ti,ab.
61.	(data adj2 envelopment*).ti,ab.
62.	system* model*.ti,ab.
63.	or/41-64
64.	quality-adjusted life years/
65.	sickness impact profile/
66.	(quality adj2 (wellbeing or well being)).ti,ab.
67.	sickness impact profile.ti,ab.
68.	disability adjusted life.ti,ab.
69.	(qal* or qtime* or qwb* or daly*).ti,ab.
70.	(euroqol* or eq5d* or eq 5*).ti,ab.
71.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
72.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
73.	(hui or hui1 or hui2 or hui3).ti,ab.
74.	(health* year* equivalent* or hye or hyes).ti,ab.
75.	discrete choice*.ti,ab.
76.	rosser.ti,ab.
77.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
78.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
79.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
80.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
81.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
82.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
83.	or/22-40
84.	21 and (38 or 63 or 83)

Table 15: Embase (Ovid) search terms

1.	diverticul*.mp.
2.	limit 1 to English language
3.	letter.pt. or letter/
4.	note.pt.
5.	editorial.pt.
6.	case report/ or case study/
7.	(letter or comment*).ti.
8.	or/3-7
9.	randomized controlled trial/ or random*.ti,ab.
10.	8 not 9
11.	animal/ not human/
12.	nonhuman/

13.	exp Animal Experiment/
14.	exp Experimental Animal/
15.	animal model/
16.	exp Rodent/
17.	(rat or rats or mouse or mice).ti.
18.	or/10-17
19.	2 not 18
20.	Economics/
21.	Value of life/
22.	exp "Costs and Cost Analysis"/
23.	exp Economics, Hospital/
24.	exp Economics, Medical/
25.	Economics, Nursing/
26.	Economics, Pharmaceutical/
27.	exp "Fees and Charges"/
28.	exp Budgets/
29.	budget*.ti,ab.
30.	cost*.ti.
31.	(economic* or pharmaco?economic*).ti.
32.	(price* or pricing*).ti,ab.
33.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
34.	(financ* or fee or fees).ti,ab.
35.	(value adj2 (money or monetary)).ti,ab.
36.	or/20-35
37.	statistical model/
38.	*theoretical model/
39.	nonbiological model/
40.	stochastic model/
41.	decision theory/
42.	decision tree/
43.	exp nursing theory/
44.	monte carlo method/
45.	(markov* or monte carlo).ti,ab.
46.	econom* model*.ti,ab.
47.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
48.	((organi?ation* or operation* or service* or concept*) adj3 (model* or map* or program* or simulation* or system* or analys*)).ti,ab.
49.	(econom* adj2 (theor* or system* or map* or evaluat*)).ti,ab.
50.	(SSM or SODA).ti,ab.
51.	(strateg* adj3 (option* or choice*) adj3 (analys* or decision*)).ti,ab.

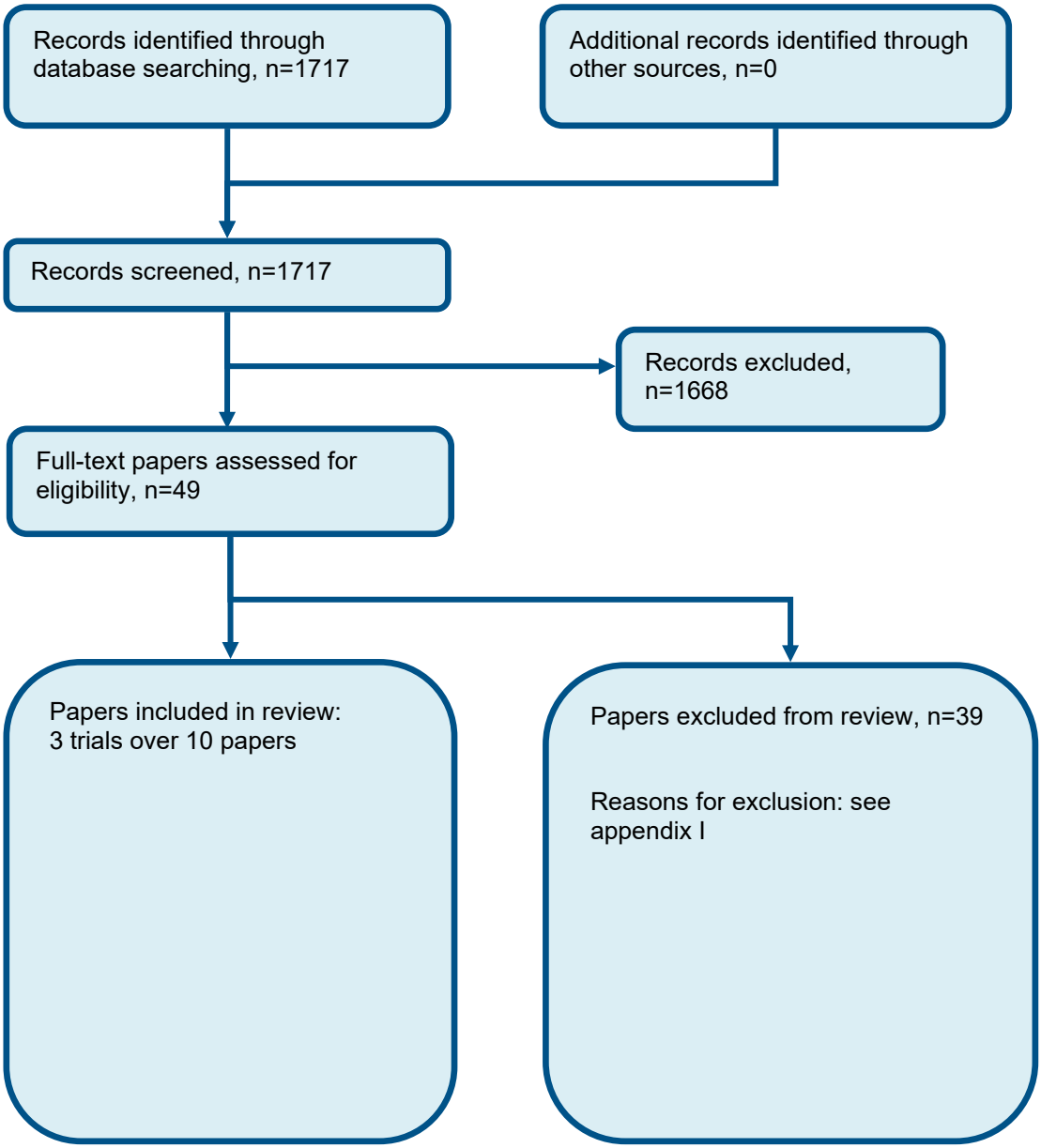
52.	soft systems method*.ti,ab.
53.	(Meta-heuristic* or Metaheuristic*).ti,ab.
54.	(dynamic* adj2 (model* or system*)).ti,ab.
55.	(simulation adj3 (model* or discrete event* or agent)).ti,ab.
56.	(microsimulation* or "micro* simulation*").ti,ab.
57.	((flow or core) adj2 model*).ti,ab.
58.	(data adj2 envelopment*).ti,ab.
59.	system* model*.ti,ab.
60.	or/39-61
61.	quality adjusted life year/
62.	"quality of life index"/
63.	short form 12/ or short form 20/ or short form 36/ or short form 8/
64.	sickness impact profile/
65.	(quality adj2 (wellbeing or well being)).ti,ab.
66.	sickness impact profile.ti,ab.
67.	disability adjusted life.ti,ab.
68.	(qal* or qtime* or qwb* or daly*).ti,ab.
69.	(euroqol* or eq5d* or eq 5*).ti,ab.
70.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
71.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
72.	(hui or hui1 or hui2 or hui3).ti,ab.
73.	(health* year* equivalent* or hye or hyes).ti,ab.
74.	discrete choice*.ti,ab.
75.	rosser.ti,ab.
76.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
77.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
78.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
79.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
80.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
81.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
82.	or/20-40
83.	19 and (36 or 60 or 82)

Table 16: NHS EED and HTA (CRD) search terms

#1.	diverticul*

Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review of laparoscopic lavage versus resectional surgery



Appendix D: Clinical evidence tables

Table 17: Clinical evidence tables

Study (subsidiary papers)	**DILALA trial: Angenete 2016[6] (Gehrman 2016[20], Thornell 2016[49], Thornell 2011[50], Kohl 2018[26])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	2 (n=83)
Countries and setting	Conducted in Denmark, Sweden; Setting: Surgical department in 9 hospitals
Line of therapy	1st line
Duration of study	Intervention + follow up: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: acute perforated diverticulitis confirmed by imaging; intra-abdominal gas or free fluid.
Stratum	overall
Subgroup analysis within study	Stratified then randomised
Inclusion criteria	Inclusion of patients was based on radiologic examination of the abdomen showing intra-abdominal fluid or gas and a decision to perform surgery followed by the patient's informed consent.
Exclusion criteria	The exclusion criteria were as follows: patients not possible to operate due to concomitant disease or patients participating in another randomized trials in conflict with the protocol and end points of the DILALA trial.
Age, gender and ethnicity	Age - Mean (range): lavage group 62 (18-86,) hartmann group 68 (35-88). Gender (M:F): lavage group 21/18,

	hartmann group 15/21. Ethnicity:
Further population details	
Indirectness of population	No indirectness
Interventions	(n=43) Intervention 1: Laparoscopic lavage. Laparoscopic lavage of all 4 quadrants was performed with saline, 3 L or more, of body temperature, until clear fluid was returned.. Duration follow up of 12 months. Concurrent medication/care: A passive drain was placed in the pelvis in all patients and left in place for at least 24 hours. Both groups were treated postoperatively according to local routines regarding antibiotic treatment, thrombosis prophylaxis and return to oral feeding.. Indirectness: No indirectness (n=40) Intervention 2: Resectional surgery . Open Hartmann procedure was performed through a midline incision. All specimens underwent pathology examination.. Duration follow up 12 months. Concurrent medication/care: A passive drain was placed in the pelvis in all patients and left in place for at least 24 hours. Both groups were treated postoperatively according to local routines regarding antibiotic treatment, thrombosis prophylaxis and return to oral feeding.. Indirectness: No indirectness
Funding	Other (ALF; Sahlgrenska University hospital, Gothenburg)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LAPROSCOPIC LAVAGE versus RESECTIONAL SURGERY

Protocol outcome 1: Quality of life at Define
- Actual outcome: EuroQol-5D VAS at 12 months;
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5; Group 2 Number missing: 5

Protocol outcome 2: Mortality at Define
- Actual outcome: Deaths at 12 months; Group 1: 6/43, Group 2: 6/40
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover -

Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5; Group 2 Number missing: 5
- Actual outcome: Deaths at 24 months; Group 1: 6/43, Group 2: 7/40
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5; Group 2 Number missing: 5

Protocol outcome 3: Morbidity at Define
- Actual outcome: adverse events at 12 months; Group 1: 28/43, Group 2: 20/40
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5; Group 2 Number missing: 5

Protocol outcome 4: Complications (abscesses) at Define
- Actual outcome: Abscess at 12 months; Group 1: 11/43, Group 2: 6/40
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5; Group 2 Number missing: 5

Protocol outcome 5: Rehospitalisation at Define
- Actual outcome: Unplanned hospital readmission at 12 months; Group 1: 7/43, Group 2: 0/40
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0
- Actual outcome: hospital readmission (planned/unplanned) at 24 months; Group 1: 19/43, Group 2: 12/40; Comments: summary of people with diverticulitis related readmission at 12 months and people with digestive system related readmissions at 12-24 months
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 6: Need for further intervention (surgery, percutaneous drain) at Define
- Actual outcome: Patients with ≥1 reoperations at 12 months; Group 1: 12/43, Group 2: 25/40
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5; Group 2 Number missing: 5
- Actual outcome: Patients with ≥1 reoperations at 24 months; Group 1: 18/43, Group 2: 27/40
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5; Group 2 Number missing: 5

Protocol outcome 7: Stoma formation at Define - Actual outcome: Stoma formation at 12 months; Group 1: 2/43, Group 2: 1/40 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5; Group 2 Number missing: 5 - Actual outcome: Stoma at 12 months at 12 months; Group 1: 3/43, Group 2: 11/40 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5; Group 2 Number missing: 5 - Actual outcome: Stoma formation up to 24 months (excluding formation as part of the index operation); Group 1: 3/43, Group 2: 2/40; Comments: These values represent the number of stomas formed during the 24 month period, not the total number of the stomas present at the end of the 24 month period and it also doesn't take into account the number of stoma reversals during this period. Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5; Group 2 Number missing: 5 - Actual outcome: Stoma at end of follow-up at 24 months and 12 months; Group 1: 3/43, Group 2: 9/40 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5; Group 2 Number missing: 5	
Protocol outcomes not reported by the study	Progression of disease at Define; Complications (infections) at Define; Complications (perforation) at Define; Complications (fistula) at Define; Complications (stricture) at Define; Anastomotic leak rate at Define

Study (subsidiary papers)	LADIES trial: Vennix 2015[53] (Swank 2010[48], Vennix 2017[54])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=90)
Countries and setting	Conducted in Belgium, Italy, Netherlands; Setting: Hospitals
Line of therapy	1st line
Duration of study	Intervention + follow up: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Radiological examination by radiography or a CT scan showing diffuse-free intraperitoneal air or fluid
Stratum	overall
Subgroup analysis within study	Not applicable
Inclusion criteria	People with perforated diverticulitis
Exclusion criteria	People with dementia, previous sigmoidectomy, pelvic irradiation, chronic treatment with high dose steroids, aged under 18 years and over 85 years.
Age, gender and ethnicity	Age - Mean (SD): lavage: 62.3 (12.7), resection: 64 (12.3. Gender (M:F): Define. Ethnicity:
Further population details	
Extra comments	2 weeks results for quality of life, mean (SD): EQ-5D VAS was 65.3 (16.3) for the lavage group and 58.9 (18.5) for the resection group. SF36 physical was 37.5 (7.6) and 34.3 (6.0), and SF36 mental was 42.3 (11.4) and 43.2 (11.4) for lavage and resection groups respectively.

Indirectness of population	No indirectness
Interventions	(n=47) Intervention 1: Laparoscopic lavage. Laparoscopic lavage was done by irrigation with 6 L of warm saline, a Douglas drain was inserted in the right lateral port site. . Duration 12 months follow-up. Concurrent medication/care: All patients given 7 days antibiotic post-procedure. 4-6 weeks after lavage, sigmoidoscopy was done to exclude malignancy. (n=43) Intervention 2: Resectional surgery. Hartmann's procedure or Sigmoidectomy with primary anastomosis was done according to the guidelines of the American Society of Colon and Rectal Surgeons. the creation of a defunctioning ileostomy was at the discretion of the surgeon. . Duration 12 months follow-up. Concurrent medication/care: All patients given 7 days antibiotic post-procedure. 4-6 weeks after lavage, sigmoidoscopy was done to exclude malignancy. Patients were offered stoma reversal if they were fit enough for another surgical procedure. . Indirectness: No indirectness
Funding	Academic or government funding (Netherlands organisation for health research and development)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LAPROSCOPIC LAVAGE versus RESECTIONAL SURGERY

Protocol outcome 1: Quality of life at Define
- Actual outcome: EQ-5D- VAS at 6 months; Group 1: mean 74.2 (SD 14.1); n=32, Group 2: mean 73 (SD 17.4); n=32; EQ-5D 0-100 Top=High is good outcome
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 15; Group 2 Number missing: 11
- Actual outcome: SF-36 physical component at 6 months; Group 1: mean 46.3 (SD 7.9); n=32, Group 2: mean 44.8 (SD 8); n=32; SF-36 0-100 Top=High is good outcome
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 15; Group 2 Number missing: 11
- Actual outcome: SF-36 mental component at 6 months; Group 1: mean 48.3 (SD 11.2); n=32, Group 2: mean 48.1 (SD 9.9); n=32
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 15; Group 2 Number missing: 11

Protocol outcome 2: Mortality at Define
- Actual outcome: mortality at 12 months; Group 1: 4/46, Group 2: 6/42
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 1

Protocol outcome 3: Morbidity at Define
- Actual outcome: Overall morbidity at upto12 months; Group 1: 30/46, Group 2: 20/42
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments - ; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 1

Protocol outcome 4: Progression of disease at Define
- Actual outcome: Recurrent diverticulitis at 12 months; Group 1: 9/46, Group 2: 1/42
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 1

Protocol outcome 5: Complications (infections) at Define
- Actual outcome: Wound infection at 12 months; Group 1: 2/46, Group 2: 9/42
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 1

Protocol outcome 6: Complications (abscesses) at Define
- Actual outcome: Abscess without drainage at 12 months; Group 1: 4/46, Group 2: 3/42
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 1

Protocol outcome 7: Rehospitalisation at Define
- Actual outcome: Hospital readmission at 12 months; Group 1: 18/46, Group 2: 19/42
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 1

Protocol outcome 8: Need for further intervention (surgery, percutaneous drain) at Define
- Actual outcome: surgical reintervention at 12 months; Group 1: 21/46, Group 2: 27/42

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Very high, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1; Group 2 Number missing: 1	
Protocol outcomes not reported by the study	Complications (perforation) at Define; Complications (fistula) at Define; Complications (stricture) at Define; Anastomotic leak rate at Define; Stoma formation at Define

Study (subsidiary papers)	SCANDIV trial: Schultz 2015[44] (Schultz 2017[43])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=)
Countries and setting	Conducted in Norway; Setting: Hospital
Line of therapy	1st line
Duration of study	Intervention + follow up: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: diagnostic imaging results (via an abdominal CT scan) showing free air and findings compatible with perforated diverticulitis (usually including colonic wall thickening and pericolic inflammation)
Stratum	overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Inclusion criteria included patient ability to tolerate general anaesthesia and diagnostic imaging results (via an abdominal CT scan) showing free air and findings compatible with perforated diverticulitis (usually including colonic wall thickening and pericolic inflammation). The indication for surgery was presence of clinical peritonitis.
Exclusion criteria	Exclusion criteria were bowel obstruction and pregnancy.
Age, gender and ethnicity	Age - Mean (SD): Lavage: 68.5 (13.4), resection 64.9 (15.0). Gender (M:F): Define. Ethnicity:
Further population details	
Extra comments	The decision to operate was made by the surgeon in charge, a position that varied between hospitals from

	senior surgical residents to colorectal attending surgeons.
Indirectness of population	No indirectness
Interventions	(n=89) Intervention 1: Laparoscopic lavage. In laparoscopic lavage, pneumoperitoneum was preferably obtained by an open transumbilical technique with a 12-mm trocar, using at least 2 additional 5 mm trocars for abdominal access. All quadrants were rinsed before placing a non-suction drain on each side of the pelvis. Adhesions to the sigmoid were not to be dissected.. Duration 12 months follow up. Concurrent medication/care: All patients were administered intravenous antibiotics, according to local practices, after a diagnosis of peritonitis was established. In both groups, the time to drain removal was determined by the surgeon. According to the protocol, the abdominal cavity in all patients was rinsed with at least 4 L of saline or until drainage was clear.. Indirectness: No indirectness (n=85) Intervention 2: Resectional surgery . the choices of laparoscopic versus open resection, and also of Hartmann procedure versus primary resection and anastomosis (PRA) were determined by surgeon preference and local practices.. Duration 12 months. Concurrent medication/care: All patients were administered intravenous antibiotics, according to local practices, after a diagnosis of peritonitis was established. In both groups, the time to drain removal was determined by the surgeon. According to the protocol, the abdominal cavity in all patients was rinsed with at least 4 L of saline or until drainage was clear.. Indirectness: No indirectness
Funding	Academic or government funding (South-Eastern Norway Regional Health Authority, Akershus University Hospital)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LAPROSCOPIC LAVAGE versus RESECTIONAL SURGERY

Protocol outcome 1: Quality of life at Define
- Actual outcome: Cleveland global quality of life score at 12 months; Group 1: mean 0.73 (SD 0.026); n=63,
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover

- Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 26; Group 2 Number missing: 29

Protocol outcome 2: Mortality at Define
- Actual outcome: Death from any cause at 12 months; Group 1: 9/74, Group 2: 8/70
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 15; Group 2 Number missing: 15

Protocol outcome 3: Morbidity at Define
- Actual outcome: All severe complication at 12 months; Group 1: 30/89, Group 2: 22/83
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 2

Protocol outcome 4: Progression of disease at Define
- Actual outcome: recurrence of diverticulitis at 12 months; Group 1: 9/74, Group 2: 1/70
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 15; Group 2 Number missing: 15

Protocol outcome 5: Complications (infections) at Define
- Actual outcome: surgical infection at 12 months; Group 1: 25/74, Group 2: 21/70
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 15; Group 2 Number missing: 15

Protocol outcome 6: Complications (abscesses) at Define
- Actual outcome: intra-abdominal abscess at 12 months; Group 1: 15/74, Group 2: 7/70
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 15; Group 2 Number missing: 15

Protocol outcome 7: Rehospitalisation at Define
- Actual outcome: unplanned readmissions at 12 months; Group 1: 26/74, Group 2: 16/70
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 15; Group 2 Number missing: 15

Protocol outcome 8: Need for further intervention (surgery, percutaneous drain) at Define - Actual outcome: reoperations at 12 months; Group 1: 21/74, Group 2: 20/70 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 15; Group 2 Number missing: 15	
Protocol outcomes not reported by the study	Complications (perforation) at Define; Complications (fistula) at Define; Complications (stricture) at Define; Anastomotic leak rate at Define; Stoma formation at Define

Appendix E: Forest plots

E.1 Laparoscopic lavage versus resectional surgery

Figure 2: Quality of life: Cleveland score, 12 months

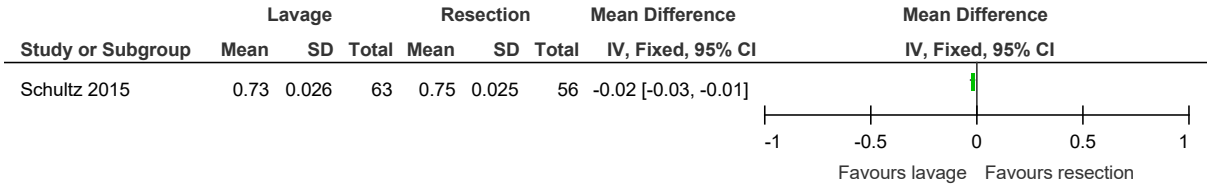


Figure 3: Quality of life: EQ5D 3L VAS, 6 months

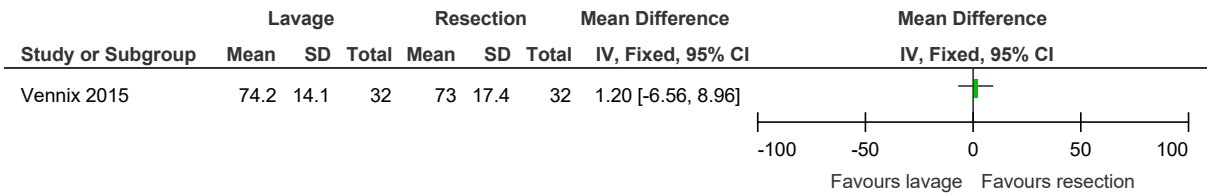


Figure 4: Quality of life: SF-36, 6 months

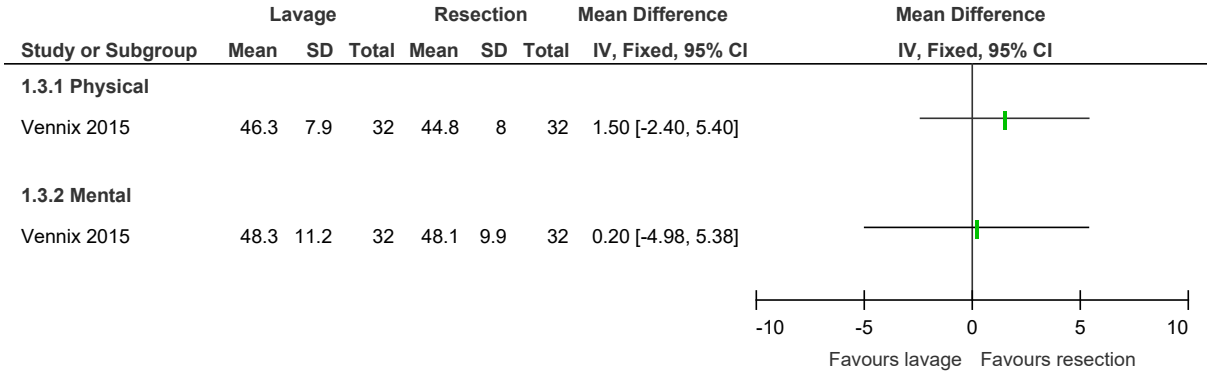
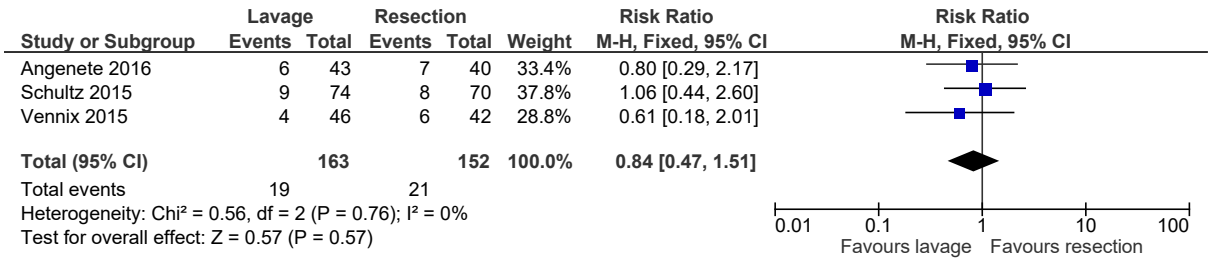


Figure 5: Mortality, end of follow-up



Note: Angenete 2016: 24 months, Schultz 2015 and Vennix 2015: 12 months follow-up

Figure 6: Morbidity/adverse events, 12 months

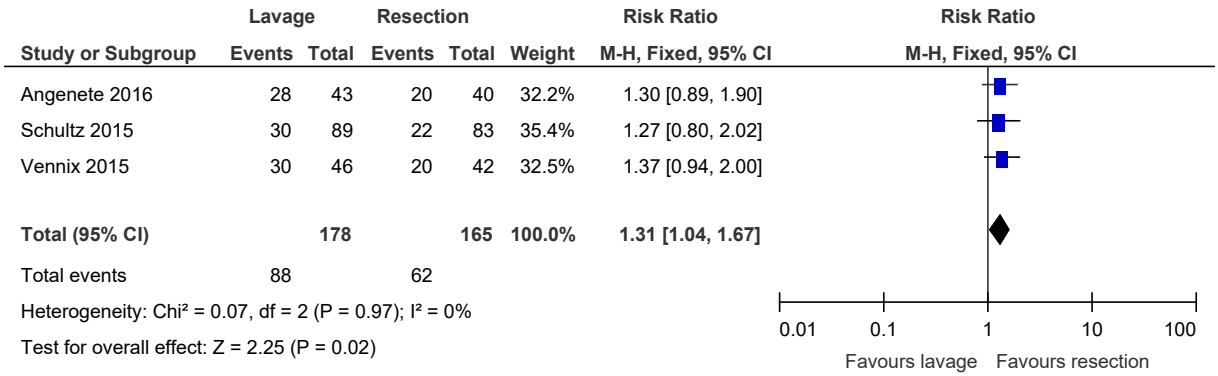


Figure 7: Progression of disease: recurrent diverticulitis, 12 months

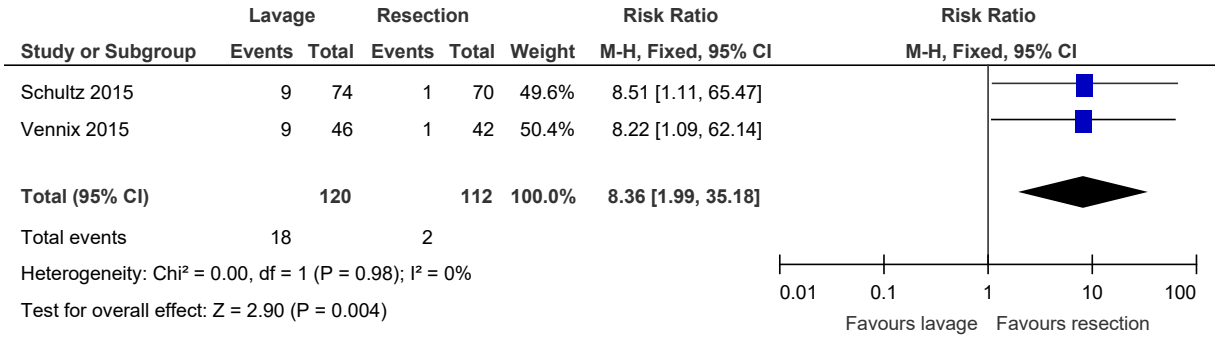


Figure 8: Complication: abscess, 12 months

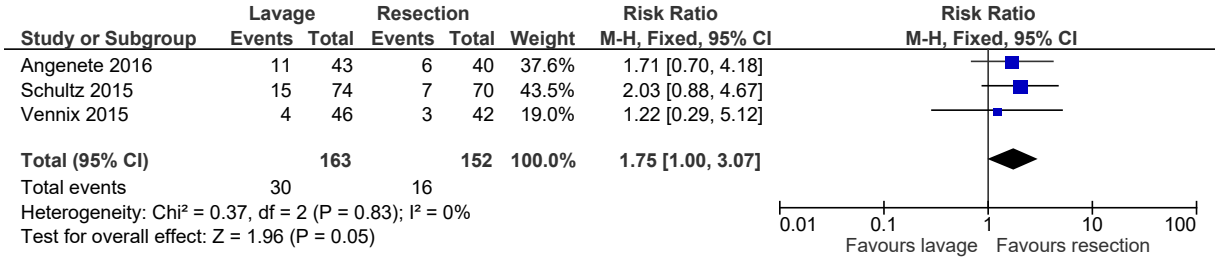


Figure 9: Complications: infection, 12 months

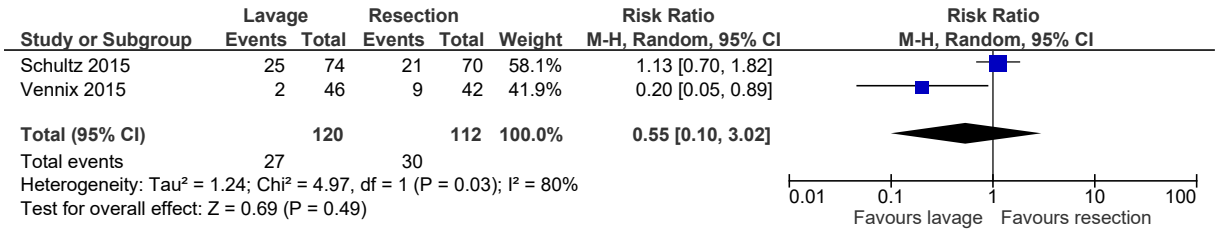
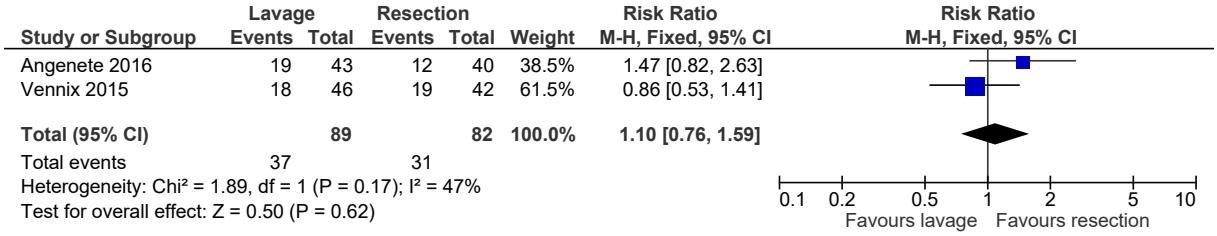


Figure 10: Rehospitalisation: hospital admissions, end of follow-up



Note: Angenete 2016: 24 months and Vennix 2015: 12 months follow-up. Forest plot represents planned and unplanned admissions.

Figure 11: Unplanned hospital admissions at 12 months

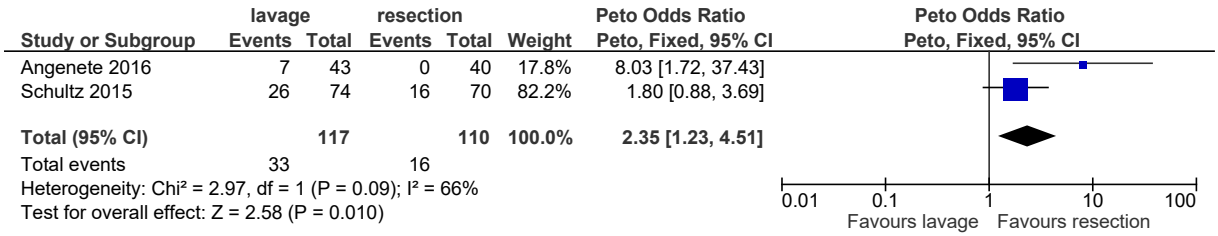
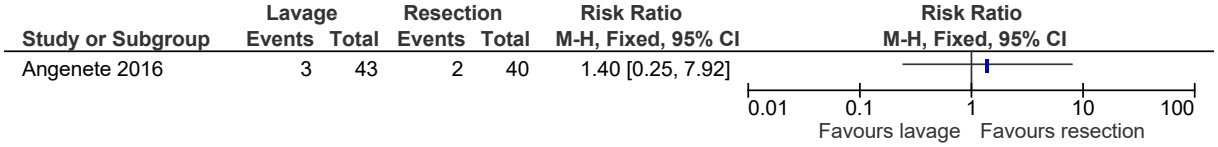


Figure 12: Further interventions: reoperations, end of follow-up

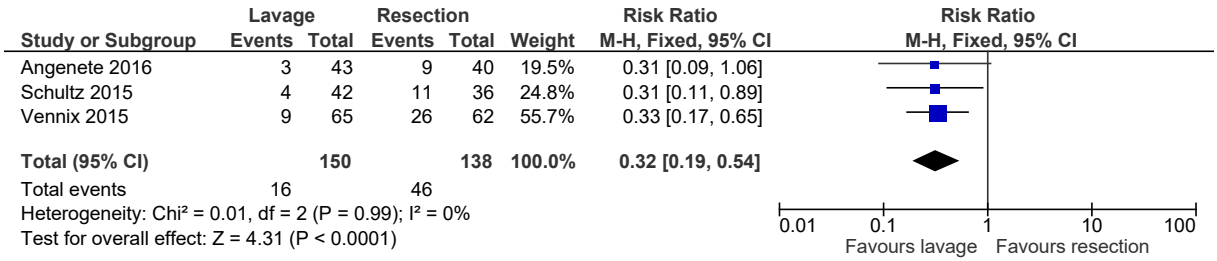
Note: Angenete 2016: 24 months, Schultz 2015 and Vennix 2015: 12 months follow-up

Figure 13: Stoma formation during 24 months (excluding formation in index surgery)



Note: These values represent the number of stomas formed during the 24 month period, not the total number of the stomas present at the end of the 24 month period and it also doesn't take into account the number of stoma reversals during this period.

Figure 14: Stoma at end of follow-up



Note: Angenete 2016: 24 months, Schultz 2015 and Vennix 2015: 12 months follow-up

Appendix F: GRADE tables

Table 18: Clinical evidence profile: laparoscopic lavage versus resectional surgery

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lavage versus resectional surgery	Control	Relative (95% CI)	Absolute		
Quality of life-Cleveland quality of life score 12 months (follow-up 12 months; range of scores: 0-1; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	63	56	-	MD 0.02 lower (0.03 to 0.01 lower)	⊕⊕⊕O MODERATE	CRITICAL
Quality of life- EQ5D 3L VAS 6 months (follow-up 6 months; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	serious	no serious indirectness	very serious[2]	none	32	32	-	MD 1.2 higher (6.56 lower to 8.96 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life- SF36 6 months - Physical (follow-up 6 months; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	32	32	-	MD 1.5 higher (2.4 lower to 5.4 higher)	⊕⊕OO LOW	CRITICAL
Quality of life- SF36 6 months - Mental (follow-up 6 months; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	32	32	-	MD 0.2 higher (4.98 lower to 5.38 higher)	⊕⊕OO LOW	CRITICAL
Mortality at end of follow-up												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	19/163 (11.7%)	11.9%	RR 0.84 (0.47 to 1.51)	19 fewer per 1000 (from 63 fewer to 61 more)	⊕OOO VERY LOW	CRITICAL
Morbidity/adverse events 12 months (follow-up 12 months)												

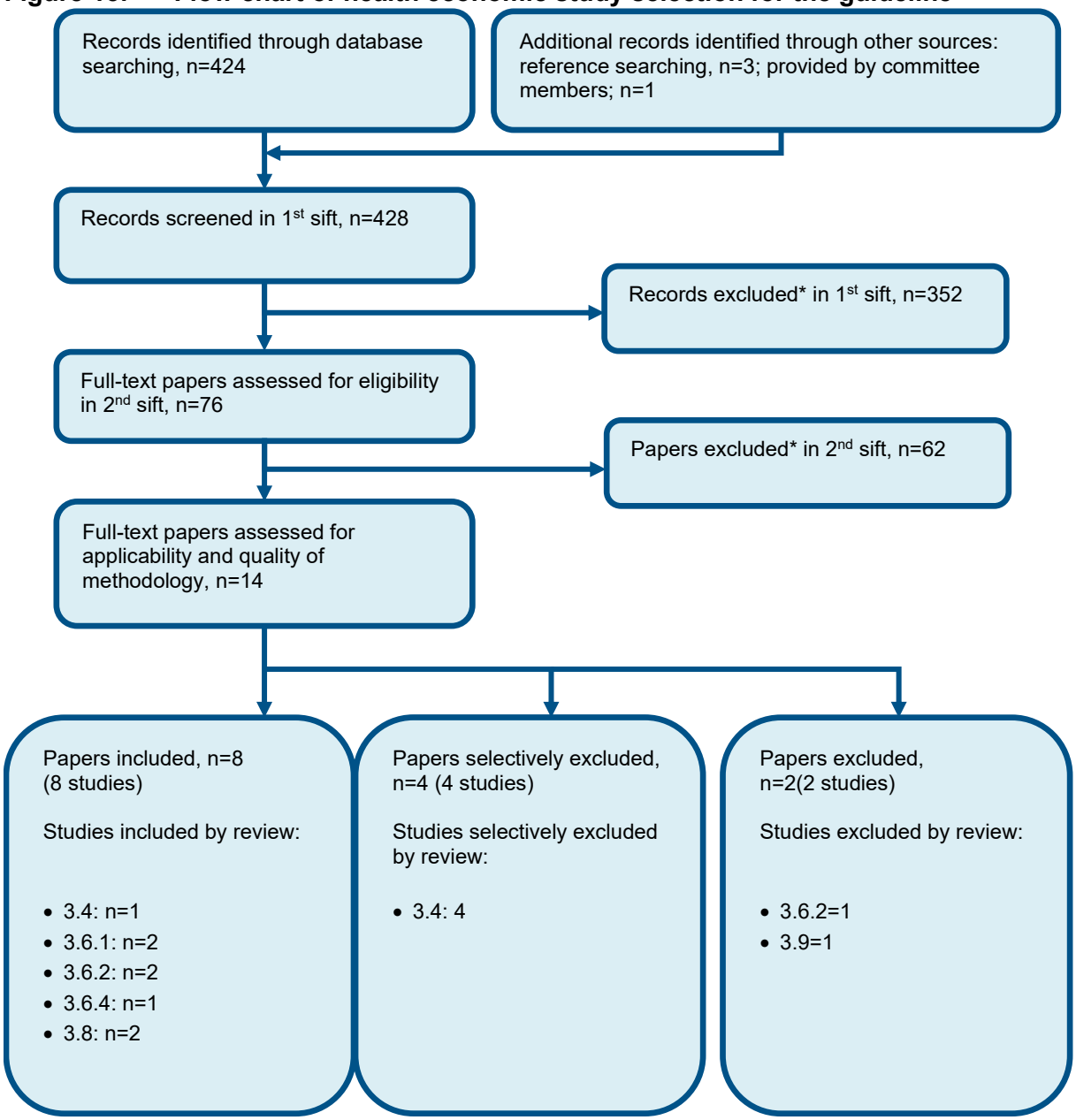
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	88/178 (49.4%)	47.6%	RR 1.31 (1.04 to 1.67)	148 more per 1000 (from 19 more to 319 more)	⊕⊕⊕O MODERATE	CRITICAL
Progression of disease: recurrent diverticulitis 12 months (follow-up 12 months)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	18/120 (15%)	1.9%	RR 8.36 (1.99 to 35.18)	140 more per 1000 (from 19 more to 649 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Complication: Abscess 12 months (follow-up 12 weeks)												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	21/163 (12.9%)	4.8%	RR 1.75 (1 to 3.07)	36 more per 1000 (from 0 more to 99 more)	⊕⊕OO LOW	CRITICAL
Complication: infections 12 months (follow-up 12 months)												
2	randomised trials	serious[1]	serious[4]	no serious indirectness	very serious[3]	none	27/120 (22.5%)	25.7%	RR 0.55 (0.10 to 3.02)	116 fewer per 1000 (from 231 fewer to 519 more)	⊕OOO VERY LOW	CRITICAL
Hospital readmission at end of follow-up												
1	randomised trials	no serious risk of bias	serious[5]	no serious indirectness	very serious[2]	none	37/89 (41.6%)	45.2%	RR 1.1 (0.76 to 1.59)	45 more per 1000 (from 108 fewer to 267 more)	⊕OOO VERY LOW	CRITICAL
Unplanned hospital readmissions (follow-up 12 months)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	33/117 (28.2%)	11.4%	OR 2.35 (1.23 to 4.51)	118 more per 1000 (from 23 more to 253 more)	⊕⊕OO LOW	CRITICAL
Reoperations 12 months (follow-up 12 months)												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	59/163 (36.2%)	62.5%	RR 0.74 (0.59 to 0.95)	162 fewer per 1000 (from 31 fewer to 256 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Stoma formation excluding formation as part of the index operation (follow-up 24 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	3/43 (7%)	2.5%	RR 1.4 (0.25 to 7.92)	10 more per 1000 (from 19 fewer to	⊕⊕OO LOW	CRITICAL

										173 more)		
Stoma at 12 months (follow-up 12 months)												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	16/150 (10.7%)	30.6%	RR 0.32 (0.19 to 0.54)	208 fewer per 1000 (from 141 fewer to 248 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs. MID is 0.03 for EQ5D.
[3] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs.
[4] The point estimate varies widely across studies, unexplained by subgroup analysis.
[5] Downgraded by 1 or 2 increments because the point estimate varies widely across studies.

Appendix G: Health economic evidence selection

Figure 15: Flow chart of health economic study selection for the guideline



* Non-relevant population, intervention, comparison, design or setting; non-English language

3.4 Non-surgical treatment of acute diverticulitis (Evidence review H)

3.6.1 Timing of surgery (Evidence review J)

3.6.2 Laparoscopic versus open resection (Evidence review K)

3.6.4 Primary versus secondary anastomosis (Evidence review M)

3.8 Laparoscopic lavage versus resection for perforated diverticulitis (Evidence review O)

3.9 Management of recurrent diverticulitis (Evidence review P)

Appendix H: Health economic evidence tables

Table 19: Health economic evidence tables

Study	Gehrman, 2016[20]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CCA (health outcome: (EQ-5D VAS, mortality, morbidity, reoperation, abscess, stoma at 1 year) **Study design:** Within-trial analysis of DILALA RCT with post-trial extrapolation. **Approach to analysis:** Unit costs were derived from Swedish sources and were applied to the resource use data from the DILALA RCT. A decision tree was used to model the costs for people with a stoma after 12 months in the Hartmann's procedure arm. A decision tree was used to model the costs for people undergoing resection in the laparoscopic lavage arm. Two time horizons were considered: base-case A- 1 year; base-case B- lifetime. **Perspective:** Sweden, healthcare sector **Time horizon:** Lifetime **Treatment effect duration:**[(a)] 1 year	**Population:** People with perforated diverticulitis with purulent peritonitis (Hinchey grade III) **Patient characteristics:** Included patients: Intervention 1: 40 Intervention 2: 43 Start age, median (IQR): Intervention 1: 68 (56-79) Intervention 2: 64 (50-76) Male: Intervention 1: 40% Intervention 2: 49% **Intervention 1:** Hartmann's procedure **Intervention 2:** Laparoscopic lavage	**Total costs (mean per patient):** Intervention 1: £43,377 Intervention 2: £24,505 Incremental (2−1): Saves £18,871 (95% CI: Saves £33,042 - £4,701; p=0.010) **Currency & cost year:** 2016 Euros (presented here as 2016 UK pounds[(b)]) **Cost components incorporated:** Laparoscopic equipment, surgical equipment (vessel-sealing instruments, stapling instrument, suture materials, laparoscopic ports, saline), anaesthesia, time in recovery room, number of transfusions, length of stay, number of reoperations and subsequent length of stay, colonoscopy in laparoscopic lavage group during year 1 following surgery, diagnostic colonoscopy for those in Hartmann's procedure group undergoing stoma reversal, antibiotic costs (3 days of intravenous piperacillin and tazobactam; 7 days oral metronidazole and cephalosporin)	**EQ-5D VAS, 1 year:** Intervention 1: 88 (SD: 75-72) Intervention 2: 83 (SD: 60-90) Incremental (2−1): 5 lower (95% CI: NR; p=NR) **Mortality, 1 year:** RR: 0.93 [95% CI: 0.33 to 2.65] **Morbidity, 1 year:** RR: 1.30 [95% CI: 0.89 to 1.90] **Abscess, 1 year:** RR: 1.71 [95% CI: 0.70 to 4.18] **Further intervention, 1 year:** RR: 0.45 [95% CI: 0.26 to 0.76] **Stoma, 1 year:** RR: 0.25 [95% CI: 0.08 to 0.84]	**ICER (Intervention 2 versus Intervention 1):** n/a **Analysis of uncertainty:** One-way sensitivity analysis was performed on the costs of (varied by 30%) to assess the impact on the results. Robustness was demonstrated through varying the costs for each variable for base case B (lifetime time

Discounting: Costs: NR; Outcomes: NR		for infectious adverse events		horizon).

Data sources

Health outcomes: Treatment effects and baseline risks from the DILALA RCT [49]. **Quality-of-life weights:** EQ-5D VAS **Cost sources:** Antibiotic and stoma material unit costs were pharmacy retail prices. Equipment costs were from the region Västra Götaland, Sweden. Unit costs of anaesthesia, transfusion, time in recovery room, length of stay and colonoscopy and readmissions were by interview with an economist at Sahlgrenska University Hospital. The unit costs of reoperation, elective readmission and sigmoidectomy were from the national cost per patient database of the Swedish Association of Local Authorities and Regions. Resource use data were reported from all nine centres in Sweden and Denmark included in the DILALA RCT. Re-usable laparoscopic equipment resource use was estimated by personnel from Sahlgrenska University Hospital, costed and divided by the number of procedures undertaken from 2013-2014 to obtain a cost per procedure. Resource use for disposable instruments and saline was collected individually. Resource items per day for stoma care were estimated by a specialised stoma nurse.

Comments

Source of funding: Swedish Research Council, the Agreement concerning research and education of doctors, Health and Medical Care Committee of the Regional Executive Board and Region Västra Götaland and Sahlgrenska University Hospital Health Technology Assessment Centre. **Limitations:** Some unit costs obtained by interview with an economist at Sahlgrenska University Hospital. Time in intensive care unit was excluded from the cost analysis because it was deemed unrelated to the underlying surgical technique. Discounting of costs and outcomes not reported. Quality of life assessment did not include pre-operative baseline questionnaires due to severity of disease on admission; a baseline evaluation at discharge was recorded. Stoma reversal included in numbers for reoperation. Percutaneous drainage of an abscess not classed as reoperation (biases this outcome towards laparoscopic lavage). Only infectious adverse events occurring within 90 days were assumed to be related to the intervention. In the decision tree for laparoscopic lavage, of the patients modelled to have sigmoid resection, 25% were assumed to have anastomosis with diverting ileostomy which is removed within 3 months (no permanent stomas). The remaining 75% were modelled to have anastomosis without diverting ileostomy (no permanent stomas). In the decision tree for Hartmann's procedure, 75% of stomas are never reversed. Of the people undergoing stoma reversal, 13% have a new stoma. One author reported grants from the Swedish Research Council and Mary von Sydow Foundation outside of the published work (no other conflicts of interest were declared). **Other:** Anastomosis not included in intervention 1, so all people have a stoma. In DILALA, laparoscopic lavage was demonstrated to be more effective and less costly so no cost effectiveness analysis was warranted. EQ-5D questionnaire data not shown, but stated to show no significant changes over time in either group. SF-36 data not shown.

Overall applicability: Partially applicable(c) **Overall quality:** Potentially serious limitations(d)

Abbreviations: CCA: cost–consequences analysis; 95% CI: 95% confidence interval; da: EQ-5D VAS: Euroqol 5 dimensions Visual Analogue Scale (self-rated scale: 0-100 where 1 is the worst imaginable health status and 100 is the best imaginable health status); ICER: incremental cost-effectiveness ratio; NR: not reported; RR: risk ratio; SD: standard deviation

(a) To extrapolate the treatment effect beyond the treatment effect duration to the lifetime time horizon in the Hartmann's procedure arm, a decision tree was constructed with probabilities based on assumptions. Stoma reversal later than 12 months was assumed to occur in 25% of people. Reversal was assumed to be successful in 86% of cases, with 13% requiring a new stoma and death (1%).Probabilities for stoma management were obtained from a population-based study for non-reversal, successful reversal, failed reversal and creation of another stoma and death. To extrapolate the treatment effect beyond the treatment effect duration to the lifetime time horizon in the laparoscopic lavage arm, it was assumed that 25% of people would later require a resection. 75% of these people were assumed to undergo anastomosis and creation of a loop ileostomy, while 25% were assumed to have a stoma which was assumed to be reversed in all cases after 3 months.

(b) Converted using 2016 purchasing power parities[35]

(c) Directly applicable / Partially applicable / Not applicable

(d) Minor limitations / Potentially serious limitations / Very serious limitations

Study	Vennix, 2017 [54]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome: QALYs, quality of life (EQ-5D VAS, SF-36), mortality, morbidity) **Study design:** Within-trial analysis of LADIES RCT with post-trial extrapolation to lifetime time horizon for costs. **Approach to analysis:** Resource use per patient in LOLA arm of LADIES RCT multiplied by unit costs to calculate total costs per patient. Dutch government 2012 tables used to estimate life expectancy following surgery. Decision tree model used to calculate costs over remaining years of life. **Perspective:** The Netherlands, societal **Time horizon:** lifetime (costs); 1 year	**Population:** People with suspected perforated diverticulitis, clinical signs of general peritonitis and radiological findings of diffuse free intraperitoneal air or fluid. Hinchey III (in LOLA arm of trial). **Patient characteristics:** Included patients: Intervention 1: 42 Intervention 2: 46 Start age, mean (SD): Intervention 1: 64.0 (12.3) Intervention 2: 62.3 (12.7) Male: Intervention 1: 60% Intervention 2: 57% **Intervention 1:** Sigmoid resection	**Total costs (mean per patient), up to 1 year:** Intervention 1: £24,600 Intervention 2: £21,611 Incremental (2−1): Saves £2,989 (95% BCaCI: -£13,634 to £6,935; p=NR) **Total costs (mean per patient),1 year – end of life:** Intervention 1: £37,829 Intervention 2: £32,400 Incremental (2−1): Saves £5,342 (95% BCaCI: -£22,316 to £10,362; p=NR) **Total costs (mean per patient), lifetime:** Intervention 1: £62,429 Intervention 2: £54,012 Incremental (2−1): Saves £8,417 (95% BCaCI: NR; p=NR) **Currency & cost year:** 2012 euros (presented here as 2012 UK pounds[(b)])] **Cost components incorporated:** Direct medical costs: Ward and intensive care unit stay, costs of primary interventions and re-interventions (including reusable instruments and disposables, personnel costs and overheads), diagnostic imaging,	**QALYs (mean per patient), 1 year:** Intervention 1: NR Intervention 2: NR Incremental (2-1): 0.032 QALYs lost (95% BCaCI: 0.147 lost to 0.081 gained; p= NR) **Quality of life, 6 months (SF-36 Physical):** Intervention 1: 44.8 (SD: 8) Intervention 2: 46.3 (SD: 7.9) Incremental (2−1): 1.5 higher (95% CI: 2.4 lower to 5.4 higher; p=NR) **Quality of life, 6 months (SF-36 Mental):** Intervention 1: 48.1 (SD: 9.9) Intervention 2: 48.3 (SD: 11.2) Incremental (2−1): 0.2 higher (95% CI: 4.98 lower to 5.38 higher; p=NR) **EQ-5D VAS, 6 months:** Intervention 1: 73 (SD: 17.4 Intervention 2: 74.2 (SD: 14.1) Incremental (2−1): 1.2 higher (95% CI: 6.56 lower to 8.96	**ICER (Intervention 2 versus Intervention 1), 1 year:** £166,811 per QALY gained (pa) 95% BCaCI: dominant to £1,574,491 Probability Intervention 2 cost effective (€30,000 per QALY gained willingness-to-pay threshold): 14.7% **ICER (Intervention 2 versus Intervention 1), 1 year:** £93,618 per poor outcome averted (major morbidity and mortality at 1 year) (pa) 95% BCaCI: dominant to £808,522 Probability Intervention 2 cost effective (€30,000 per poor outcome averted willingness-to-pay threshold): 20.9% **Analysis of uncertainty:** One way sensitivity analysis of probabilities and some unit costs subgroups by ±20% (hospital stay including ward and intensive care unit, stoma-associated

(QALYs) **Treatment effect duration:**[(a)] 6 months (quality of life); 1 year (costs and other health outcomes) **Discounting:** Costs: NR; Outcomes: NR	with or without anastomosis **Intervention 2:** Laparoscopic Lavage	readmissions, stoma care, stoma reversal surgery and related admissions, outpatient consultation visits (surgeon, gastroenterologist, general practitioner, physiotherapist or company physician), formal home care (assistance with household tasks, personal care or nursing). Direct non-medical costs: travel expenses and informal home care.	higher; p=NR) **Mortality, 1 year:** RR: 0.61 [95% CI: 0.18 to 2.01] **Morbidity, 1 year:** RR: 1.37 [95% CI: 0.94 to 2.00]	costs and acute or elective relaparotomy) and ±50% (costs of the primary interventions). Total cost difference (1 year) varied in sensitivity analyses on costs between intervention 2 saves £2,135 and intervention 2 saves £3,777

Data sources

Health outcomes: Treatment effects and baseline risks from the LADIES RCT.[53] **Quality-of-life weights:** EQ-5D Dutch tariff **Cost sources:** Unit costs were from the Dutch guideline on unit costing in healthcare, the Hospital Costs ledger 2012 from the Academic Medical Centre, Amsterdam and based on top-down calculations. The primary interventions were costed using a bottom-up approach. Mean costs in the sigmoid resection group were calculated based on the ratio of different procedures undertaken (e.g. open or laparoscopic; colostomy, ileostomy or none). If costs differed between academic and non-academic hospitals, the costs were applied to the respective patients. Resource use was recorded in the study clinical record forms or retrieved from patient-reported questionnaire responses at 1, 3, 6, 9 and 12 months.

Comments

Source of funding: Netherlands Organisation for Health Research and Development **Limitations:** Some resource use patient-reported, obtained from questionnaire responses. Direct non-medical costs of travel expenses and informal home care included, differing from NICE Reference Case. For the within-trial portion of the analysis, quality of life reported at 6 months was extrapolated to 12 months. Discounting not reported. Quality of life with EQ-5D incorrectly calculated in accompanying trial publication as an average of scores across 3 dimensions, reported as a 'health state'. [53]Unclear whether EQ-5D 'health state' data or EQ-5D VAS data were used in the calculation of QALYs at 1 year, used to calculated the ICER. **Other:** No difference was shown in mortality, morbidity or quality of life so the pre-specified cost-effectiveness and cost-utility analyses were not expected to be useful and were therefore only briefly described.

Overall applicability: Partially applicable[(c)] **Overall quality:** Potentially serious limitations[(d)]

Abbreviations: 95%BCaCI: bias-corrected and accelerated confidence intervals; 95% CI: 95% confidence interval; CUA: cost–utility analysis; EQ-5D: Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); EQ-5D VAS: Euroqol 5 dimensions Visual Analogue Scale (self-rated scale: 0-100 where 1 is the worst imaginable health status and 100 is the best imaginable health status); ICER: incremental cost-effectiveness ratio; NR: not reported; pa: probabilistic analysis; QALYs: quality-adjusted life year; RR: risk ratio; SD: standard deviation

(a) To extrapolate from the treatment effect duration to the lifetime time horizon for costs, Dutch government 2012 tables were used to estimate life expectancy following surgery. A decision tree model was used to calculate costs over remaining years of life, incorporating probability of stoma reversal surgery (30%) and success rate (93%), reversal-related mortality (1%), probability of recurrent diverticulitis (35% for those without sigmoid resection, 5% for those with sigmoid resection), risk of abdominal wall hernia for laparoscopic (21 per 1000 patient-years) and open (39 per 1000 patient-years) surgery and subsequent probability of resection (15%). Probability assumptions were informed by published observational studies.

(b) Converted using 2012 purchasing power parities[35]

(c) Directly applicable / Partially applicable / Not applicable

(e)*Minor limitations / Potentially serious limitations / Very serious limitations*

Appendix I: Excluded studies

I.1 Excluded clinical studies

Table 20: Studies excluded from the clinical review

Study	Exclusion reason
Alamili 2009[1]	Systematic review: study designs inappropriate
Ambrosetti 1993[2]	Incorrect interventions
Ames 2009[3]	No relevant outcomes
Angenete 2010[5]	Not in English
Angenete 2017[4]	Systematic review: included studies individually included
Angriman 2010[7]	Incorrect interventions
Barry 2012[8]	Not review population
Bartels 2010[9]	Incorrect interventions
Binda 2018[11]	Inappropriate comparison
Boermeester 2016[12]	No relevant outcomes
Boselli 2016[13]	Non-randomised study
Ceresoli 2016[14]	Systematic review: methods are not adequate/unclear
Cirocchi 2013[16]	Systematic review: methods are not adequate/unclear
Cirocchi 2017[15]	Systematic review: studies individually included
Gaertner 2013[18]	Inappropriate comparison
Galbraith 2017[19]	Systematic review: studies individually included
Gervaz 2016[21]	No relevant outcomes
Gralista 2017[22]	Systematic review: methods are not adequate/unclear
Haas 2016[23]	Incorrect interventions
Kang 2012[24]	Not review population. Incorrect interventions
Kaushik 2016[25]	No relevant outcomes

Kronborg 1986[27]	Inappropriate comparison
Lam 2009[28]	Non-randomised study
Liang 2012[29]	Not guideline condition
Marshall 2017[30]	Systematic review: methods are not adequate/unclear
Medina-fernandez 2015[31]	Incorrect interventions. Inappropriate comparison
Neumann 1991[33]	Not in English
Parisi 2016[36]	Non-randomised study
Penna 2018[37]	Systematic review: study designs inappropriate
Ponzano 2017[38]	Conference abstract
Regenbogen 2014[39]	No relevant outcomes
Russ 2010[40]	No relevant outcomes
Sammour 2011[41]	Incorrect interventions
Schmidt 2018[42]	Systematic review: methods are not adequate/unclear
Senapati 1995[45]	No relevant outcomes
Shaikh 2017[46]	Systematic review: studies individually included
Spasojevic 2012[47]	No relevant outcomes
Thorson 2012[51]	Incorrect interventions
Toorenvliet 2010[52]	Systematic review: study designs inappropriate