NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology consultation: Endo-SPONGE for treating low rectal anastomotic leakage

Supporting documentation – Committee papers

The enclosed documents were considered by the NICE medical technologies advisory committee (MTAC) when making their draft recommendations:

1. **EAC assessment report** – an independent report produced by an external assessment centre who have reviewed and critiqued the available evidence.
2. **Assessment report overview** – an overview produced by the NICE technical lead which highlights the key issues and uncertainties in the company's submission and assessment report.
3. **Scope of evaluation** – the framework for assessing the technology, taking into account how it works, its comparator(s), the relevant patient population(s), and its effect on clinical and system outcomes. The scope is based on the sponsor's case for adoption.
4. **Adoption scoping report** – produced by the adoption team at NICE to provide a summary of levers and barriers to adoption of the technology within the NHS in England.
5. **Sponsor submission of evidence** – the evidence submitted to NICE by the notifying company.
6. **Expert questionnaires** – expert commentary gathered by the NICE team on the technology.
7. **EAC correspondence log** – a log of all correspondence between the external assessment centre (EAC) and the company and/or experts during the course of the development of the assessment report.
8. **Company fact check comments** – the manufacturer's response following a factual accuracy check of the assessment report.

Please use the above links and bookmarks included in this PDF file to navigate to each of the above documents.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technologies guidance

MT461 Endo-SPONGE for treating colorectal anastomotic leak

External Assessment Centre report

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Number of attached appendices: 6

Purpose of the assessment report

The purpose of this External Assessment Centre (EAC) report is to review and critically evaluate the company's clinical and economic evidence presented in the submission to support their case for adoption in the NHS. The report may also include additional analysis of the submitted evidence or new clinical and/or economic evidence. NICE has commissioned this work and provided the template for the report. The report forms part of the papers considered by the Medical Technologies Advisory Committee when it is making decisions about the guidance.

Declared interests of the authors

Description of any declared interests with related companies, and the matter under consideration. See NICE's Policy on managing interests for board members and employees.

None

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Responsibility for report

The views expressed in this report are those of the authors and not those of NICE. Any errors are the responsibility of the authors.

Contents

Abbreviations

Term	Definition
AL	Anastomotic Leak
CI	Confidence interval
DHSC	Department of Health and Social Care
EAC	External Assessment Centre
EVT	Endoluminal Vacuum Assisted Therapy
IPAA	Ileal pouch-anal anastomosis
IQR	Interquartile range
MAUDE	Manufacturer and User Facility Device Experience
MHRA	Medicines & Healthcare products Regulatory Agency
MTEP	Medical Technologies Evaluation Programme
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NICE CG	NICE clinical guideline
NICE MTG	NICE medical technology guidance
NICE QS	NICE quality standard
PD	Percutaneous drainage
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QUORUM	Quality of Reporting of Meta-analyses
RCT	Randomised controlled trial
SD	Standard deviation
VAC	Vacuum assisted closure
VAS	Visual analogue scale
Vs	Versus

Executive summary

The company submission included evidence from 3 systematic reviews and 20 observational studies. The EAC excluded the systematic reviews and included an additional 2 observational studies and 3 abstracts.

The published studies were considered to be at high risk of bias and the evidence relating to Endo-SPONGE was considered to be very low quality for all outcomes however due to the small number of patients who develop anastomotic leak it is unlikely that the quality of evidence can be improved.

Overall, the clinical evidence suggests that Endo-SPONGE is a safe and effective method for treating anastomotic leaks in patients who have had colorectal surgery with a high rate of success for closure of cavity and stoma reversals and a low rate of complications and mortality. As the number of patients who develop an anastomotic leak is very small however, the study sample sizes are always likely to be small and this may impact certainty around the evidence for effectiveness.

The economic analysis suggests that conservatively Endo-SPONGE may not be cost saving in year one but savings would be realized over a 10 year time horizon. Although there is considerable uncertainty around the economic model inputs and subsequent cost savings, the impact of this uncertainty is minimised by the small number of patients likely to be treated.

Some consideration should be given to Endo-SPONGE treatment being done in endoscopy units and the possible resource implications.

Decision problem

The company has not proposed any variation to the decision problem outlined in the scope.

1 Overview of the technology

Endo-SPONGE (B. Braun) is a CE marked, class IIa medical device. It is a minimally invasive vacuum treatment for anastomotic leakage in the low colorectal area after colorectal surgery. The Endo-SPONGE system uses vacuum therapy, which is commonly used for the treatment of chronic and complex wounds. The EAC notes that both the scope and the MedTech Innovation Briefing (NICE MIB188) document state that Endo-SPONGE is a class IIb device however, the declaration of conformity certificate submitted by the company lists it as a class IIa device. The EAC contacted the company who clarified that the class IIb relates to the CE certificate covering all of their wound closure devices. Endo-sponge itself is a class IIA device as stated on the declaration of conformity.

The Endo-SPONGE system consists of an open pore sponge with a Redon drain, a sponge pusher and silicon overtube guides.

The Endo-Sponge system is provided as a pack of 5 0r 10 and a separate, controllable wound drainage system, as a pack of 10 bottles. Each bottle has two pressure settings with the less powerful setting (setting 1) used for Endo-SPONGE as setting 2 is uncomfortable for patients. Each system is individually wrapped and sterile with a 5 year shelf life. Once opened, the system must be used or disposed of and no part of the system is re-usable.

The company claims that the open pores of the sponge allow for suction to be transferred evenly over all tissue in contact with the sponge and the negative pressure system promotes healing and cavity size reduction through granulation of tissue. The company additionally claims that Endo-SPONGE can reduce the risk of infection and if the area is already infected Endo-SPONGE can be used to rapidly control the infection through active drainage.

2 Clinical context

Anastomotic leaks are defined as a leak of lumenal contents from a surgical join between hollow viscera. They are serious complications of colorectal surgery and can lead to ongoing infection, development of sepsis and death. The rate of anastomotic leak rate following colorectal or coloanal surgery varies between 5% and 19% (McDermott et al. 2015) and a number of risk factors have been identified including male sex, tumour size/stage, whether a patient has emergency surgery or not, history of radiotherapy (McDermott et al. 2015). There is no clearly defined management pathway. Treatment is based on a number of factors including patient condition, anastomotic defect size and location, indication for primary resection and presence of a proximal stoma.

Guidance for the management of anastomotic leak (McDermott et al. 2016) states that patients considered to be clinically stable may be treated conservatively using fluids, antibiotics and oxygen with close clinical observation. For patients showing signs of sepsis, steps should be taken to remove the source of the leak within 3 to 18 hours (McDermott et al. 2016).

Special considerations, including issues related to equality

The NICE scope identified special considerations including that people who have been diagnosed with cancer and chronic diseases may be considered disabled under the Equality Act and colorectal anastomotic leakage is more common in men; gender is a protected characteristic under the equality act.

The company did not identify any additional concerns or considerations.

One clinical expert noted that there were possible contraindications to the use of Endo-SPONGE. Contraindications noted by clinical experts include patients with a pouch and patients with extremely low leaks although this will likely be dependent on the individual patient.

3 Clinical evidence selection

3.1 *Evidence search strategy and study selection*

The EAC consider the company's search strategy to be of low quality. Although the company searched 5 databases, the use of free text terms was limited and indexed terms were not incorporated into the search strategies; details are provided in appendix A. The EAC also noticed an error in spelling in the company literature search which may have impacted the search findings although the EAC corrected this spelling error when running the searches and did not identify any major discrepancies.

To ensure that all relevant evidence had been identified, the EAC conducted their own systematic search, to include periods from database inception to 9th January 2020. Four bibliographic databases and 2 clinical trial registries were searched using a range of free text terms and (where appropriate) subject headings. The company's website was also searched for additional literature. The MHRA's medical device alerts and field safety notices were searched for adverse events. Details of the EAC search are provided in appendix A.

3.2 *Included and excluded studies*

The EAC searches identified largely the same studies as those included in the company submission. There were some discrepancies however; details of the EAC's included studies and rationale compared with the company submission are outlined in Appendix A. In total, the EAC included 2 additional studies (Schiffman et al. 2019 and Wasmann et al. 2019), 3 additional abstracts compared with the company submission (DiMitri et al. 2010; Martel et al. 2013; and McAuley et al. 2013). The EAC also excluded 3 systematic reviews which were included in the company submission (Clifford et al. 2019; Popivanov et al. 2019 and Shalaby et al. 2019) as they were considered to be low quality, the EAC used the source literature for data extraction (appendix B) The EAC were aware that the published systematic reviews included most of the individual studies also included by the company, this caused concerns in that the inclusion of both the systematic reviews and individual studies would result in an over interpretation of the clinical evidence.

Table 1: Studies selected by the EAC as the evidence base

Study name, location, duration	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
Full text				

Study name, location, duration	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
Arezzo (2015) Italy (single centre) November 2008 to June 2013	Retrospective Case series. Endo-SPONGE. Device replaced two or three times a week until complete healing of dehiscence was achieved. All chronic cases were treated as outpatient; acute were initiated on inpatient basis and discharged if the general conditions were favourable to proceed as outpatient. Minimum follow-up – 1 year Authors declare no conflicts of interest. Status of study: published. Endo-SPONGE ● No comparator ●	N=14 (5 male, 9 female). Median age 68 years old (range 55-85). 12 leaks after rectum anterior resection, 1 leak after transanal endoscopic microsurgery and 1 recto-vaginal fistula after a stapled transanal resection of the rectum. Median distance from the anal verge was 5 cm (range 3-9 cm). Radiotherapy used in 7/14 (50%). Derivative stoma in 8/14 (57.1%). Chronic leak in 4/14 (28.6%) Median cavity length 4cm (2-9cm) Single centre Inclusion criteria: all patients with acute or chronic leak in the presence of extraluminal abscess (November 2008 – June 2013) Exclusion criteria: presence of generalized peritonitis or haemodynamically unstable patient was a contraindication to endoscopic treatment ●	Success rate (direct endo-scopic examination with the aid in all cases of direct water soluble contrast infection during endoscopy, showed a complete restoration of the wall epithelium.) Reasons for treatment failure Time to complete healing Number of sessions required (treatment sessions) ●	Small case series, retrospective design, single centre. No comparator. Data in text and table don't match (sex distribution). One patient presented with recto-vaginal fistula.

Boschetti (2018) France (2 centres) January 2013 to December 2016	Retrospective case series January 2013 to December 2016 Endo-SPONGE Endo-SPONGE treatment was started in the month following surgery in 12 cases, and the mean delay was 35±56 weeks (8-260 weeks) in the remaining cases. These were cases referred from other centres due to failure of surgical or radiological treatments. Patients followed up endoscopically at 1, 3 and 6 months after treatment Authors report no conflict of interest Status of study: published. Endo-SPONGE ● No comparator ●	N=29 patients (22 male, 7 female) Mean age 68±10 years (range 51 – 88) 23 with rectal cancer and 19 with neo-adjuvant chemoradiotherapy 3 sigmoiditis (1 left colonic cancer, 2 right colonic cancer with peritoneal carcinosis treated by hyperthermic intraperitoneal chemotherapy and left colectomy with colorectal anastomosis) Fistula was detected after sepsis in 25/29 (86.2%) patients, rectal bleeding in 6.9% (n=2), and diarrhoea in 3.4% (n=1). Mean fistula length was 7cm±4.6cm (2-20cm) Mean distance from anal verge was 6.2cm±4.6cm (2-20cm) At inclusion stage, 21 patients were referred for Endo-SPONGE treatment with a stoma systematically performed at the time of anastomosis (n=12) or secondly to treat sepsis (n=9). N=12 patients were taking antibiotics when Endo-SPONGE was performed Nutritional support was used in 3 patients	Unclear,the outcomes are not defined in the methods of the study but the results report: Time to closure Number of sessions Success rate Reversal of protective stoma ●	Retrospective Small sample size No comparator

Huisman (2019) Netherlands (2 centres) January 2012 to August 2017	Retrospective Case series. Endo-SPONGE with surgical closure (surgical closure at the preference of the surgeon). Depending on size of cavity 1-3 were placed in deepest point of presacral cavity with pressure of 150 mmHg, sponges were change twice/week. At 1st placement surgeon and gastroenterologist placed sponges, subsequent placements were made by gastroenterologist alone. Depending on surgeon preference, transanal closure of the defect was performed after a short period of Endo-SPONGE therapy (vacuum-assisted early transanal closure) to achieve shorter Endo-SPONGE therapy duration. Start of follow-up was primary resection and end of follow-up was date of interest; stoma reversal date, last Endo-SPONGE exchange date, date of death or end of follow-up. End of follow-up for patients without stoma reversal or not censored was last hospital visit. Median follow-up was 10 months (3-84) Authors declare no conflict of interest.	N=20 (14 male, 6 female); median age 64 years (SD 10). Indication: 18 rectal cancer; 2 inflammatory bowel disease. 2 colorectal cancer centres. Jan 2012 to Aug 2017. Inclusion/exclusion criteria: all eligible patients with symptomatic AL after rectal surgery treated with Endo-SPONGE therapy were included. Patients with postoperative signs of AL and AL confirmed by computed tomography (CT) scan were considered eligible. Patients with colonic cancer, patients who underwent Hartmann's procedure as primary surgical procedure and patients who underwent transanal endoscopic microsurgery (TEM) were excluded. ●	Primary outcome: restored gastrointestinal continuity at end of follow-up. ● Secondary outcomes: success rate; presence of a chronic sinus and the functional bowel outcome after AL (LARS score). ●	The study intervention was Endo-Sponge alone or Endo-SPONGE followed by a surgical closure of defect for some patients. Small case series (high risk of bias). No comparator.

Study name, location, duration	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
	Status of study: published. Endo-SPONGE + Surgical closure 🟡 no comparator 🔴			

Jiménez Rodríguez (2018) Spain (single centre Study period not reported	Case series. (unclear, possibly prospective) Endo-SPONGE. Depending on size of cavity 2 or more were used. Initially pressure of 375 mmHg was used and modified to 150 mm Hg at the first sponge replacement, sponges were changed every 3 – 5 days. In all patients, the first treatment was performed in-hospital, but the successive replacements were carried out on an outpatient basis for 11 patients. For 10 patients fibrin glue was used in addition after VAC therapy was over and once the diameter of the cavity was too small to allow entry of the sponge. Follow-up began at the time treatment stopped following cavity closure. Mean follow-up period was 12.36±7.9 months Funding provided by Instituto de Salud Carlos III, Madrid, Spain. Status of study: published. Endo-SPONGE ● No comparator ●	N=22 (18 male, 4 female); median age 64.8 years (SD 9.90). Indication: colorectal cancer, 13 underwent anterior resection and colorectal anastomosis, and 9 underwent Hartmann's procedure Tertiary hospital. Dates of procedure/data collection not provided. Inclusion/exclusion criteria: patients scheduled to undergo VAC therapy for dehiscence of lower colorectal anastomosis or opening of the rectal stump after anterior resection for rectal cancer were included. Patients with severe signs of systemic inflammatory response that needed immediate intensive treatment were excluded as were those with cavities that had a size less than 2 × 2 cm. ●	The following were recorded: complications during the procedure and until wound healing was complete, recurrence rate in cases of cancer, mortality rate, and length of hospital stay, number of devices used in each patient, the number of days of treatment, the size of the cavity at onset of therapy, the number of days elapsing from surgery to the diagnosis of anastomotic dehiscence or rectal stump leakage, and those from diagnosis to the end of therapy. ●	Small case series (high risk of bias). No comparator. Dates of procedure/data collection not provided. For 10 patients fibrin glue was used after VAC therapy (once diameter of the cavity was too small to insert a sponge) – this is not related to the success of the endo-SPONGE treatment.

Study name, location, duration	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
Katz (2018) Israel (single centre) May 2014 to December 2016	Retrospective Case series. Endo-SPONGE. In 5 cases insertion was manual (under sedation) and in 1 case via TAMIS approach (under general anaesthesia) after the failure of endoscopic insertion. All procedures were performed in the operating room. A diverting stoma was constructed in 2/3 patients who had no previous diversion. One patient was treated with endo-sponge and antibiotics with no need for diversion. No patient underwent irradiation prior to treatment. Median duration of follow-up was 28 months (18-32) Authors declare no conflict of interest. Status of study: published. Endo-SPONGE 🟢 No comparator 🔴	N= 6 (5 male, 1 female); median age 63 years (SD 20.3). Indications as follows: low rectal cancer; rectal villous adenoma; Hirschsprung; familial adenomatous polyposis; ovarian cancer with rectal involvement. Median dehiscence 180 (degrees) range 50-270 degrees Median time to leak diagnosis 7 days (range 4-14 days). Median time to first sponge placement 13 days (range 9-33) Hospital. May 2014 to Dec 2016. Inclusion/exclusion criteria: not reported. 🟢	A priori outcome measures not reported in the methods. Results include reporting of • success rate • restoration of bowel continuity • number of sponge exchanges 🔴	Very small case series (high risk of bias). No comparator. Inclusion/exclusion criteria not reported. Discrepancy in reporting of stoma numbers between table and text of the study (table suggests 3/5 had a stoma already and 1/5 had a stoma created following leak diagnosis).

Study name, location, duration	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
Keskin (2015) Turkey (single centre) May 2009 to May 2014	Retrospective Case series Endo-SPONGE. Applied in an endoscopy unit under sedation by a surgeon. The sponge was changed every 3 – 4 days. Average number of sponge applications was 2.2 (range, 1 to 5). 12 patients treated as in-patients and 3 as out-patients. Follow-up duration period not reported. Authors declare no conflict of interest. Status of study: published. Endo-SPONGE ● No comparator ●	N=15 (8 female, 7 male), average age 55 years (25-72). Indications: rectal tumour (n=12); familial polyposis coli (n=2); diverticular disease (n=1). Eight leaks were identified early and 7 leaks identified late Hospital (endoscopy unit) May 2009 and May 2014. Inclusion/exclusion criteria: patients deemed suitable for Endo-SPONGE treatment who developed AL after protectomy were included. Patients with cavities opening to the abdomen due to low rectal anastomotic leakages were excluded. ●	Cavity closure Results were also reported for lumen integrity, stoma closure rate, impact of early and late diagnosis on treatment success and any recurrent abscesses although these were not listed as outcomes in the methods ●	Small case series (high risk of bias). No comparator.

Study name, location, duration	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
Kuehn (2016) Germany (single centre) 2007-2015	Retrospective Case series. Endo-SPONGE. Inpatient or outpatient therapy. Placement was carried out in the surgical endoscopy unit, in the operating room or on the intensive care unit. Sponges were changed after 3 days. EVT usually performed without the need for sedation or anaesthesia Mean follow-up was 36 months (2-89) Conflicts of interest not reported. Status of study: published. Endo-SPONGE ● No comparator ●	N=20. Median age of 70 years (range 29-91) of entire cohort. Indication: an extraperitoneal anastomotic leakage after rectal or rectosigmoid resection 20/20 (rectal or rectosigmoid cancer 16/20, diverticulitis 2/20, recurrent perforating diverticulitis 1/20, iatrogenic perforation 1/20). Radio- or radio-chemotherapy used in 75% of cancer patients. Single centre Inclusion criteria: patients with defects of lower gastrointestinal tract showing the signs of anastomotic leakage or rectal lesion. Considered for patients with signs of a localized peritonitis of the lower abdomen (September 2007 – February 2015) Exclusion criteria: operative revision was indicated for patients with signs of a generalized peritonitis ●	Success Closure of enterostomy and reasons for failure Adverse events Time to leakage detection Therapy duration Number of sponges used ●	Small sample size, retrospective design, single centre. No comparator. No information regarding conflict of interests.

Study name, location, duration	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
Manta 2016 Italy (2 centres) April 2009 to September 2014	Retrospective Case series. Endo-SPONGE. Periodically changed until fistula closure was achieved. The initial positioning in hospital, changes performed in outpatient setting. Single or multiple devices were used. Follow-up not reported Authors declare no conflict of interest. Status of study: published. Endo-SPONGE ● No direct comparator but some patients were treated using over the scope clips (OTSC) or OTSC plus stents. ●	N=7. Fistula type: 6 delayed, 1 early with diameter ranged 15 – 50m. 4 underwent anterior rectal resection, 2 left colectomy, 1 total colectomy. 2 Endoscopic Units, 7/7 in out-patients setting. N=18 treated with OTSC and N=4 treated with OTSCO+Stent Inclusion criteria: patients with a post-surgical leak referred by the surgeon for an initial endoscopic attempt in order to avoid re-intervention (April 2009 – September 2014). ●	Fistula closure Length of stay was an outcome for the whole study cohort but not applicable to Endo-SPONGE as these were all outpatients ●	The study was not designed to investigate what method of closure was most effective therefore comparisons have not been made between the different treatment types. Baseline characteristics were not presented for Endo-SPONGE patients only. Small case series (high risk of bias), retrospective design. Possible overlap with Strangio (2015) as one study centre is the same.

Study name, location, duration	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
Milito (2017) Italy (single centre) January 2007 to December 2014	Retrospective Case series. Endo-SPONGE. Mean anastomosis level was 5 cm (3-7). Patients received an intravenous antibiotic therapy with piperacillin+tazobactam (4.5g, 3 times/daily). Median size of the cavity was 81x46 mm Median time to leak diagnosis 14 days (range 7-21) Follow-up not reported Authors declare no conflict of interest. Status of study: published. Endo-SPONGE ● No comparator ●	n=14 (10 male, 4 female). Mean age 72 years (42-81). Indication: malignancy (rectal cancer) 14/14. Preoperative radiotherapy 14/14. Stoma created during primary surgery 14/14. Single centre Inclusion criteria: patients with anastomotic leakage following low anterior resection; dimension of the cavity >1x0.5 cm 9impossibility to insert the sponge; age of patients <85 years; rectal anastomosis <7cm from anal verge (difficult placement); loop ileostomy during the previous surgery (January 2007 – December 2014) Exclusion criteria: diffuse peritonitis; nonednoscopically accessible septic focus; malignant tumour wound; untreated osteomyelitis ●	Time to diagnosis of anastomotic leakage Time of the outpatient therapy Sponge exchanges for each patient Healing time Complications and side effects ●	Data in the table does not match information in the text (mean age) Small number of patients, observational study, single centre. Retrospective design.

Study name, location, duration	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
Mussetto (2017) Italy (single centre) March 2010 to February 2015	Retrospective Case series. Endo-SPONGE. The therapy was performed under conscious sedation (meperidine (0.5-1mg/kg IV) and midazolam (2.5-5 mg IV)). The sponges were changed every 48-72 h. Closure was defined as a decreased cavity covered with granulation tissue that did not allow the insertion of a new sponge. Mean distance of anastomosis from anal verge was 4.5 cm (range 2-8). Mean size of leakage was 7.5 cm (range 4-12). Mean follow-up was 29 months (6-64) Authors declare no conflicts of interest. Status of study: published. Endo-SPONGE ● No comparator ●	N=11 (6 male, 5 female). Mean age 71 years old (range 55 – 82). Indication: 11/11 rectal cancer. Neoadjuvant radio/chemotherapy in 5/11. Single centre Inclusion criteria: Patients with anastomotic leakage (March 2010 – February 2015) ●	Number of treatments Number of days from treatment to closure Closure of anastomotic leakage Treatment failure Relapse of leakage Complications Follow-up time Mortality ●	Small number of patients, retrospective design, single centre. No comparator. Lack of exclusion criteria.

Nerup (2013) Denmark (2 centres) February 2008 to 2012	Retrospective Case series. Endo-SPONGE. The sponge was changes every second or third day. Treatment was ceased when the cavity was about 3 cm wide and covered in granulation tissue. Median tumour distance from anus was 9 cm (6-12). Inpatient stay, some continued treatment as outpatient. Follow-up not reported Authors declare no conflicts of interest. Status of study: published. Endo-SPONGE ● No comparator ●	N=13 (11 males, 2 females). Median age was 64 years (range 36-71). ASA classification: I 4/13 (31%), II 9/13 (69%). Indication: 13/13 (100%) rectal cancer. Primary ileostomy 13/13 (100%). Neoadjuvant radiotherapy 6/13 (46%). Two centres Inclusion criteria: patients with rectal cancer following low anterior resection of the rectum who developed an anastomotic leak and were treated with endoscopic vacuum therapy; patients who could be managed without re-laparotomy (1st of Feb 2008 – 1st of Feb 2012) Exclusion criteria: late onset endoscopic vacuum treatment more than one month after leakage diagnosis and patients who had not completed treatment at 1st of Feb 2012; patients who required re-laparotomy ●	Treatment success Hospital stay Number of treatments Length of treatment Mortality Complications Stoma closure rate ●	Small number of patients, retrospective study design. Uneven sex distribution.

Study name, location, duration	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
Riss, Stift, Kienbacher (2010) Austria (six centres) 2006-2009	Retrospective Case series Endo-SPONGE. Sponges were changes at 2-3 days intervals. 1/20 had fibrin glue injection to improve healing, 1/20 has stent inserted for 7 days. Median follow-up was 17 months (1.5 to 29.8) Conflicts of interest not reported. Status of study: published. Endo-SPONGE ● No comparator ●	N=20 (13 males, 7 females). Median age was 66.3 years (range 54.8-91.2 years). 20/20 treated for rectal cancer (2/20 the upper third, 8/20 the middle third and 10/20 the lower third of the rectum). A protective stoma was created in 14/20. Neoadjuvant short-term radiotherapy in 1/20, long-term radio/chemotherapy in 5/20. Indication: 17/20 anastomotic leakage, 3/20 insufficiency of a rectal stump after Hartmann's procedure. Six surgical centres Inclusion criteria: consecutive patients who had undergone initially successful endo-sponge assisted treatment of anastomotic leakage following rectal cancer surgery (2006-2009) ●	Follow-up duration Time from primary operation to anastomotic leakage Mortality Complications Stoma reversal Duration of therapy ●	Long term follow up of patients successfully treated with Endo-SPONGE (follow-up of the patient group in Riss et al. 2009). The EAC will only report the additional, unique outcomes from the long-term follow-up. Small number of patients. Lack of comparator Use of other non-operative interventions (fibrin glue, stent) Lack of conflicts of interest statement.

Study name, location, duration	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
Riss, Stift, Meier (2009) Austria (single centre) September 2007 to June 2008	Retrospective Case series Endo-SPONGE. Applied as primary therapy or if previous treatment options failed to achieve sufficient leak control. Antibiotics were administered in case of ongoing sepsis or peritonitis. Hospitalization was only necessary in case of replacement or poor general condition. Performed under general anesthesia or moderate sedation. Sponge changes every 2-3 days. One patient showed an early anastomotic dehiscence 7 days after LAR. In all other patients (n = 8), the median time from primary surgery (LAR or Hartmann) to anastomotic leakage was 2.5 month (range: 1–24). No follow-up time reported as this is only reporting on short-term treatment outcomes Conflict of interests not reported. Status of study: published. Endo-SPONGE ● No comparator ●	N=9 (5 males, 4 females). Median age 63.5 years (range 50-71). all n=9/9 had initial anterior resection due to low rectal cancer Indication: 6/9 anastomotic dehiscence following low anterior resection, 3/9 rectal stump insufficiency following Hartmann's procedure. 1/9 neoadjuvant short-term radiotherapy, 3/9 neoadjuvant chemoradiotherapy, 1/9 had liver metastasis. 2/9 received chemoradiotherapy after the index operation. 4/6 patients after low anterior resection had protective stoma. Single centre Inclusion criteria: patients who developed an abscess in the pelvis following an anterior resection of low rectal cancer (2007 – 2008) ●	Time to anastomotic leakage Total time of treatment Duration of Endo-SPONGE replacement Complications Treatment success QoL: patient's satisfaction, alteration in daily life activity, pain sensation Mortality ●	Patients may overlap with Riss, Stift, Kienbacher (2010) therefore the EAC will only report the long term outcoems from Riss et al (2010) Small number of patients, retrospective study design, single centre. Lack of conflicts of interest statement. Some outcomes not presented separately for anastomotic leakage patients (n=9), rectal stump insufficiency n=3. Lack of detailed exclusion criteria.

Study name, location, duration	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
Rottoli (2018) Italy (single centre) March 2016 to March 2017	Prospective Case series Endo-SPONGE. The first application of the device was scheduled under deep sedation. Device was replaced every 48-72h.Antibiotic treatment was given at the time of diagnosis for at least 1 week and continues as long as necessary. Median follow was 11.6 months (6-18) after confirmation of healing of the anastomotic leak Authors declare no conflict of interests. Status of study: published. Endo-SPONGE ● No comparator ●	N=8. Median age was 37 years (18-59). Indication: 7/8 ulcerative colitis refractory to medical treatment, 1/8 familial adenomatous polyposis Single centre Inclusion criteria: patients with diagnosis of anastomotic leak (partial) after ileal pouch-anal anastomosis (IPAA); all leaks were symptomatic ad associated with signs of sepsis (March 2016 – March 2017) Exclusion criteria: a complete anastomotic dehiscence or active bleeding (either from the pouch or the presacral plane) requiring surgical intervention ●	Primary outcomes: The rate of successful healing at 6 months from the leak diagnosis Secondary outcomes: Operative time – not discussed Perioperative variables (time to anastomosis leakage diagnosis, time to Endo-SPONGE treatment and duration, hospital stay, ileostomy reversal, follow-up time, recurrence) The rate of intra- and postoperative complications The number of changes of the device before discharge ●	Small case series, single centre. Lack of baseline characteristics. Outcomes (operative time) not discussed

Schiffmann (2019) Germany (single centre) November 2007 to March 2015	Comparative cohort study (retrospective) Endo-SPONGE with neoadjuvant (nRCT) (the treatment group) vs Endo-SPONGE without nRCT (the control group) An intensified nRCT (a daily intake of capecitabine with a single dose between 1000 and 1650 mg/m^2 combined with weekly applications of irinotecan (40 mg/m^2) or oxaliplatin, and local radiation 5 days a week with a single dose of 1.8 Gy adding up to 55.8 Gy. Endo-SPONGEs were changed every 3 days. Mean tumor distance from anal verge was 5.8 cm (2-10) in the treatment and 7.4 cm (4-11) in the control group (p=0.288). Follow up time not reported Authors declare no conflict of interest. Status of study: published. Endo-SPONGE + neoadjuvant radiochemotherapy ● Endo-SPONGE – neoadjuvant radiochemotherapy	Treatment group (Endo-SPONGEin patients receiving neoadjuvant radiochemotherapy): N=11 (10 males, 1 female). Mean age 66.1 years. Mean American Society of Anesthesiologists (ASA) score 2.36. Indication: 11/11 (100%) rectal cancer. Control group (Endo-SPONGE in patients not receiving radiochemotherapy): n=8 (7 males, 1 female). Mean age 62.4 years. Mean ASA score 2.13. Indication: 5/8 (62.5%) rectal cancer, 3/8 (37.5%) colon sigmoideum cancer. Single centre Inclusion criteria: patients treated with endoscopic vacuum therapy for anastomotic leakage after rectal resection for cancer with or without nRCT. There was an indication for nRCT for all patients with rectal cancer in the lower and middle rectum with a local cancer stage T3/4 or positive lymph nodes or both (November 2007 – March 2015) ●	Primary outcomes: Mortality Treatment success (healing of anastomotic leak) Long-term preservation of intestinal continuity (the absence of a stoma after 18 months) Secondary outcomes: Number of sponges needed Length of treatment Time until closing of protective ileostomy ●	Small number of patients, retrospective study design, single centre. Lack of exclusion criteria.

Study name, location, duration	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
				
Srinivasamurthy 2013 UK (single centre) September 2007 to May 2011	Retrospective Case series. Endo-SPONGE. Used according to the manufacturer's instructions; the sponge was changes under general anaesthetic with a flexible endoscope. Each patient had one sponge per application, with exception of one occasion of double sponge placement. Median time to leak detection 29 days (range 10-115) Median follow-up time 41 months (10-45) to report ileostomy reversal Median follow-up of 17 months to report recurrent abcesses Authors declare no conflict of interest. Status of study: published. Endo-SPONGE  No comparator 	N=8 (7 males, 1 female). Median age 66.5 years old (range 45-79). Anastomosis type: 6 low rectal, 1 colo-anal, 1 ileoanal. Short course radiotherapy used in 6, radical radiotherapy for previous bladder carcinoma in 1. Single centre Inclusion criteria: all patients who underwent Endo-SPONGE treatment for extraperitoneal pelvic anastomotic leakage in our hospital between September 2007 and May 2011. 	Complete closure or reduction in the abscess cavity size Ileostomy reversal Time to stoma reversal Restoration of bowel continuity Number of sponges used Treatment period 	Small sample size, single centre. Uneven sex distribution. Lack of comparator.

Strangio (2015) Italy (single centre) September 2008 to October 2013	Case series (not reported whether retrospective or prospective) Endo-SPONGE. All patients received broad spectrum antibiotics. Single or multiple sponges inserted, a constant vacuum pressure of 150 mmHg was used. Sponges were changed every 48-72h. Changes done usually in conscious sedation with 5mg midazolam IV. Outpatient treatment after a few sponge exchanges. Median time to leak detection 17 days (range 0-102 days) Median follow-up of 9 months (5-12) for mortality Authors declare no conflicts of interest. Status of study: published. Endo-SPONGE ● No comparator ●	N=25 (18 males, 7 females). Mean age: 67 years (range 37–89). 19 underwent anterior rectal resection (18 rectal cancer, 1 rectal endometriotic nodule), 5 left colectomy (4 left-sided colon cancer, 1 acute diverticulitis) and 1 proctocolectomy for severe ulcerative colitis. For patients with colorectal resection, 8/22 had radiochemotherapy and 10/22 only chemotherapy. Median dimension of cavity was 56 mm (range 15-100mm). Anastomotic leak extended from 70 to 270 degrees and the median size of cavity was 56mm (range 15-100mm Single centre Inclusion criteria: consecutive patients presenting with anastomotic leakage following colorectal surgery, with or without protective stoma. Patients with clinical signs and symptoms suggesting an inflammatory complication confined in the pelvis (September 2008 – October 2013) Exclusion criteria: patients with signs of a generalized peritonitis or a complete anastomotic dehiscence.	Complete healing of anastomotic leakage Treatment failure requiring surgery Closure of protective ileostomy and restoration of bowel continuity Mortality Number of sponges used Time to Endo-SPONGE treatment ●	No comparator. Small case series, single centre. Possible overlap with Manta (2016).

Study name, location, duration	Design and intervention(s)	Participants and setting	Outcomes	EAC comments

van Koperen (2009) The Netherlands (multicentre) July 2006 to April 2008	Case series (not reported whether retrospective or prospective) Endo-SPONGE. The sponge is changed every 3-4 days. In 6 patients general anesthesia was used, in 3 under a light sedation. 7 patients required no sedation. Median duration between the initial surgery and the discovery of the leakage was 11 days (range 3–150 days). Median follow-up after closure of the abscess cavity was 4 months (2-16) Authors declare no conflict of interests. Status of study: published. Endo-SPONGE ● No comparator ●	N=16 (9 males, 7 females). Median age of 64 years (19-78). Indication: 13/16 malignancy (rectal cancer), 3/16 benign (ulcerative colitis). 9/13 received radiotherapy, 2/13 chemoradiation. Mean anastomosis level was 5 cm (2-8) from anal verge. 8/16 had stoma created during primary surgery. Multicentre Inclusion criteria: patients with a presacral cavity after anastomotic leakage (July 2006 – April 2008) ●	Primary outcomes: closure of the cavity The ability to close the ileostomy and factors associated with successful closure Other outcomes: Time between the initial surgery and the discovery of the leakage Time between surgery and start sponge treatment Number of sponges placed initially (first insertion) Number of sponge replacements (overall) Complications/treatment failure Follow-up after the closure of the abscess cavity ●	Small number of patients, retrospective design. Lack of detailed inclusion and exclusion criteria Some centres had only 1 patient

Wasmann (2019) The Netherlands (single centre) 2002-2017	Non-concurrent cohort study (retrospective). Endo-SPONGE. Sponges exchanged every 3 to 4 days under light sedation at the endoscopy room. Admission was not required; after discharge, outpatient appointments were made to change sponges. Transanal suture closure was performed. Anastomotic leak was detected between the 3rd and 17th day post surgery, mean 8.2 SD 3.6 days Overall median follow-up was 8 years (IQA 4-12) Median follow-up for Endo-SPONGE treatment was 4 years (IQR 3-6) Median follow-up for conventional management was 13 years (IQR 10-15) Authors declare some conflict of interests (speaker' fees for 3/8 of authors). Status of study: published. Endo-SPONGE + Surgical closure 🟡 Comparator: passive approach by diversion with ileostomy and occasional drainage of the presacral	N=22 Patient treated with conventional management "(11 male, 11 female). Mean age at IPPA surgery was 34.68 (SD 12.98). Indication: 18/22 ulcerative colitis, 4/22 inflammatory bowel disease unclassified. ASA score 1 in 7/22, 2 in 14/22 and 3 in 1/22 N=18 (12 male, 6 female). Mean age at IPPA surgery was 40.56 (SD 14.48). Indication: 17/18 ulcerative colitis, 1/18 inflammatory bowel disease unclassified. ASA score 1 in 4/18, 2 in 14/18 Single centre Inclusion criteria: consecutive ulcerative colitis or inflammatory bowel disease unclassified patients who underwent IPAA and developed anastomotic leakage (January 2010 – October 2017 for Endo-SPONGE patients) Exclusion criteria: patients with indication for IPAA due to familial adenomatour polyposis, Crohn's disease or colorectal cancer, postoperative diagnosis of Crohn's disease in the pouch, redo-pouch surgery only in the study period, anastomotic leakage detected later than 3 months after IPAA surgery, leakage treatment strategies not in accordance with early surgical	Primary and secondary (pouch failure) outcomes– not of interest 🔴 Secondary outcomes: Treatment-specific details: number of sponge changes, number of Endo-SPONGEs used, duration of treatment 🟢 Short-term results of Endo-SPONGE treatment: time from IPAA to anastomotic leakage diagnosis, time from diagnosis to starting treatment, anastomotic closure at 6 months, time from diagnosis to observed closure on imaging, complications within 90 days, time to ileostomy reversal	The study intervention was Endo-Sponge followed by surgical closure. Small non-concurrent cohort study, single centre. Conflict of interest declared

Study name, location, duration	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
	abscess cavity with subsequent wait and-see approach	closure principles, a functioning IPAA of less than 1 year, cognitive inability to reply to the questionnaire, deceased during follow-up, and nonresponders to the questionnaire.		

Study name, location, duration	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
Weidenhagen (2008): Germany (single centre) 2002-2004	Case series (retrospective) Endoscopic vacuum device (describe Endo-SPONGE without mentioning the device name). Sponges are changed every 28-72h. Mean height of the anastomosis was 5.3 cm (1-12cm) above the anal verge. The length of the cavity was between 2 and 20 cm (mean 7.4 ± 5.1). The initial management of all patients included intensive nutritional support and broad-spectrum antibiotics. Initial sponge insertion was done under sedation; later sedatives were used (2-5 mg of midazolam per session). Follow-up not reported Authors declare a conflict of interest. Status of study: published. Endo-SPONGE ● No comparator ●	N= 29 (24 male, 4 female). Mean age was 66.7 years (42-79). Indication: 22/29 rectal cancer, 3/29 rectosigmoidal cancer, 2/29 large rectal adenoma, 1/29 diverticulitis, 1/29 rectal infiltration of endometrial cancer. 9/29 received preoperative radiochemotherapy. 5/29 had diabetes, 1/29 had a chronic intake of oral steroids. Protecting stoma created in 21/29 (19/21 protecting ileostomies, 2/21 colostomies) after primary surgery, 4/29 had stoma created after the secondary procedure. Single centre Inclusion criteria: patients with an anastomotic leakage after (low) anterior resection (2002-2004) ●	Patient excluded from the treatment Time of the diagnosis The treatment duration The number of sessions Duration of hospital stay Complications The improvement of the systemic inflammatory response Healing success The incidence of stenosis Stoma closure rate and time to closure ICU stay ●	The conflict of interest between the authors and the company. Small number of patients, retrospective and observational study design, single centre. Imbalance in sex distribution. Lack of exclusion criteria.

Study name, location, duration	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
Abstracts				
Di Mitri (2010) (abstract only) Italy (single centre) January to October 2009	Case series. Endo-SPONGE. The sponge system was changed every 48-72h. Performed by experienced endoscopists and taking approximately 15 minutes. Conflicts of interest not reported. Status of study: abstract only. Endo-Sponge ● No comparator ●	N=5 (5 male). Mean age 51.6 years (range 32-67). Indication: severe ulcerative colitis 1/5, colorectal cancer 4/5. Chemo- or radiotherapy in 100% of cancer patients. Single centre Inclusion criteria: patients with diverting stoma, who underwent rectal resection for rectal cancer and severe ulcerative colitis (January 2009 – October 2009) ●	Number of sessions required Adverse event Stoma closure Symptomatic and leak recurrence ●	Abstract only. Very small number of patients. Lack of exclusion criteria. Lack of conflicts of interest statement. Single centre.

Study name, location, duration	Design and intervention(s)	Participants and setting	Outcomes	EAC comments
Martel (2018) Northern Ireland (single centre) November 2008 to January 2013	Case series. Endo-SPONGE. Conflicts of interest not reported. Status of study: abstract only. Endo-SPONGE ● No comparator ●	N=10 (8 male, 2 female). Median age 59 years old. Indication: anastomotic leaks following low anterior resection 7/10, symptomatic low pelvis cavities following ileal pouch excision 2/10 or a perforated low Hartmann's stump 1/10. Single centre Inclusion criteria: patients with anastomotic leaks or symptomatic low pelvis cavities (November 2008 – January 2013) ●	Time to treatment Median duration of treatment Number of sponge changes Adverse events Cavity closure ●	Small case series, single centre. No comparator. No detailed inclusion or exclusion criteria. Abstract only. Lack of conflicts of interest statement.
McAuley (2013) UK (single centre) January 2011 to March 2013	Case series. Endo-SPONGE. N=1 treated as outpatient, n=2 treated as inpatients. Conflicts of interest not reported. Status of study: abstract only. Endo-SPONGE ● No comparator ●	N=3 Single centre Inclusion criteria: patients complicated by a localised anastomotic leak following a laparoscopic low anterior resection (January 2011 – March 2013). ●	Number of sponge changes Cavity closure ●	Very small number of patients, single centre. No comparator. Lack of detailed exclusion and inclusion criteria. Lack of conflicts of interest statement.

Table 3: Studies included by company and excluded by the EAC

Study name and location	Design and intervention(s)	Participants	Outcomes	EAC comments
Clifford (2019)	Systematic Review. Published Endoscopic methods of leak management (including but not exclusively Endo- SPONGE) 🟡 Funding not stated Stent Endoscopic clips Vacuum assisted closure Endoscopic drainage of intra-abdominal sepsis Fibrin Glue Multimodal therapy for anastomotic bleeding	Studies which include patients with anastomotic leak following colorectal anastomosis 🟢	No pre-defined outcomes. Study is a review of the published literature reports on outcomes including but not limited to • Other endoscopic intervention • Faecal diversion • Other surgical intervention • Long-term salvage rate in patients with vacuum assisted closure of anastomotic leak 🟢	The EAC has chosen to review the individual studies relevant to the topic and not include this systematic review as it is not directly relevant and critical appraisal indicates that it is a critically low quality review (see appendix C)

Study name and location	Design and intervention(s)	Participants	Outcomes	EAC comments
Popivanov (2019)	Systematic Review and meta-analysis Published Endoluminal negative pressure therapy (ENPT) for colorectal anastomotic leaks Study suggests that “For financial reasons, an improvised version instead of the commercial set Endo-SPONGE (B.Braun, Melsungen, Germany) can be used” suggesting that interventions similar to Endo-SPONGE may be included in the review ●	Patients with leaks of low colorectal anastomosis, irrespective of the indication for operation (‘low anastomoses’ defined as those located under the pelvic peritoneum) ●	success rate (defined as complete closure of the abscess cavity) rates of complications stoma closure ●	The EAC has chosen to review the individual studies relevant to the topic and not include this systematic review as it is not directly relevant and critical appraisal indicates that it is a critically low quality review (see appendix C)

Study name and location	Design and intervention(s)	Participants	Outcomes	EAC comments
Shalaby (2019)	Systematic Review and meta-analysis Published Endoluminal negative pressure therapy (ENPT) as salvage treatment for rectal anastomotic leakage Different types of Vacuum systems including but not limited to Endo-SPONGE were included in the review 🟡	Studies evaluating the outcome of EVT in the treatment of anastomotic leakage after colorectal or coloanal anastomosis and rectal stump insufficiency following Hartmann's procedure 🟢	Success of EVT, defined as complete or partial healing of the anastomotic defect and associated cavity, Rate of stoma reversal after EVT. Duration of treatment until complete healing Complications of treatment Need for further intervention 🟢	The EAC has chosen to review the individual studies relevant to the topic and not include this systematic review as it is not directly relevant and critical appraisal indicates that it is a low quality review (see appendix C)

4 Clinical evidence review

4.1 *Overview of methodologies of all included studies*

A total of 20 full studies and 3 abstracts were included by the EAC. Most of the included studies were case series studies and did not recruit patients prospectively (table 1). All 3 abstracts (DiMitri et al. 2010; Martel et al. 2018 and McAuley et al. 2013) were non-comparative, observational studies. Of 20 fully published studies, only two included studies (Schiffmann et al. 2019 and Wasmann et al. 2019) were comparative while the remaining 18 were non-comparative, observational studies. Schiffmann et al. (2019) compares outcomes in patients treated with Endo-SPONGE who had previously been treated with neoadjuvant chemoradiotherapy with patients who had not been treated with chemoradiotherapy. Wasmann et al (2019) is a non-current cohort study comparing outcomes in patients who underwent Endo-SPONGE assisted early surgical closure versus conventional management (diversion combined with transabdominal, transgluteal, or transanal drainage of the presacral abscess cavity).

All included studies had small sample sizes ranging from 3 participants (McAuley et al. 2013) to 10 (Martel 2018) with the abstracts and from 6 (Katz 2016) to 34 participantants (Weidenhagen et al. 2008) within the full studies.

Length of follow-up was not consistently reported with some studies reporting follow-up time to mortality, follow-up time to cavity closure or follow-up time to stoma reversal. Some studies did not report a follow-up time. The length of follow-up across the studies ranged from 1.5 months (Riss et al. 2010) to 96 months (Wasmann et al. 2019) but overall follow-up time was reported variably as a mean, median or minimum follow-up time making it difficult to compare across studies.

Only one of the studies (Srinivasmurthy et al. 2013) was conducted in the UK although clinical expert advice received by the EAC suggests that Endo-SPONGE is being used in the NHS. Two abstracts reporting on the UK experience (Martel et al. 2013 and McAuley et al. 2013) were identified by the EAC. One abstract (McAuley et al. 2013) is a report of the experience with 3

patients (1 outpatient, 2 inpatient) in the UK (Northern Ireland) while the second abstract includes a total of 10 patients.

4.2 *Critical appraisal of studies and review of company's critical appraisal*

The company submission does not include a formal critical appraisal of the studies included in the clinical evidence review. There is no mention of the use of any checklist for appraising study quality. The company briefly highlights the limitations of Endo-SPONGE studies in section 5 of their submission. No details of how those limitations were assessed or their impact on the quality of the clinical evidence has been presented. In addition, the company submission has included data from studies of non-operative treatment other than Endo-Sponge. The company has used results from these studies to make comparisons between effectiveness of Endo-SPONGE and other non-operative treatment options. There is no discussion in the company submission around how the studies were selected for inclusion or around the quality or limitations of these additional studies.

The EAC has used GRADE (Grading of Recommendations, Assessment, Development and Evaluation) to rate the certainty of the body of evidence included in this Assessment Report (Appendix C) for each outcome rather than focus on the quality of individual studies. This approach takes into account study design, study quality, consistency and directness in judging the quality of evidence for each outcome (GRADE Working Group 2004). The EAC identified a number of studies of Endo-SPONGE where there was a possibility of patient overlap (Appendix A). Where possible, studies with patient overlap were compared and the most recent publication or a full study publication in the case of overlap with abstracts were included in the review. In the case of four studies (Riss et al. 2009 ; Riss et al. 2010; Manta et al. 2016 and Strangio et al. 2015) the EAC identified a possible risk of overlap of patient populations. Riss et al. (2009) and Riss et al. (2010) the EAC identified a possible risk of overlap of patient populations. Riss et al. (2009) and Riss et al. (2010) had one study centre in common and there was overlap in the time period for the studies (table 1). Manta et al. (2016) and Strangio et al. (2015) also had one centre in common and overlap in time period for data

collection. The EAC could not determine which patients or outcomes may be affected by this possible overlap and have included all four studies in the clinical review. As such, the EAC notes that this may add to uncertainty around the results of the studies.

Study Characteristics

Multiple studies report outcomes of interest including time to diagnosis (11 studies), overall success rate (21 studies), stoma/ileostomy reversal and/or restoration of bowel continuity (15 studies), number of treatment sessions/sponges (19 studies), time to stoma reversal (6 studies) treatment duration (15 studies), complications (15 studies), length of hospital stay (3 studies) and quality of life (2 studies).

Two studies (Schiffmann et al. 2019; Wasmann et al. 2019) were comparative. Schiffmann et al. (2019) reported outcomes for patients with anastomotic leaks treated with Endo-SPONGE comparing outcomes for patients receiving radiochemotherapy with patients who did not. Radiotherapy is a known risk factor for anastomotic leak, however whether it has an impact on management and healing of anastomotic leak is unclear.

Wasmann et al. (2019) reported outcomes for patients whose anastomotic leaks were treated with Endo-SPONGE, with the intention of shortening the time to surgical closure (Endo-SPONGE as an addition), comparing outcomes with a historical cohort of patients who had been treated without Endo-SPONGE.

The quality of the included studies is very low for all reported outcomes. This is due primarily to the fact that all studies are at high risk of bias because they are retrospective, non-comparative case series studies and all with very small sample sizes although the EAC acknowledge that with a low rate of anastomotic leak following colorectal surgery, study sample sizes would be expected to be small. Other factors affecting the quality of the outcome data include the fact that the outcome and how it is measured is not always clearly defined in each study and the same outcome may be reported differently across the studies. The primary outcome in most studies is successful treatment with Endo-SPONGE however the individual studies have defined success differently or, in the case of 2 studies (Kuehn et al. 2016; Schiffman et al. 2019) did not report a definition for success. Most frequently studies defined successful treatment either as closure of cavity to <1cm as in Boschetti et al.,2018), as a reduction of cavity with complete granulation as in

Huisman et al., 2019 or as sufficient granulation as in Keskin et al. (2016) (see table 1). In addition to variability in how outcomes are defined, there is substantial variability across the studies in terms of whether the mean or median values are reported.

Study Populations

Sample sizes in all of the studies were small, ranging from 3 participants (McAuley et al., 2013) to 10 (Martel et al, 2018) in the abstracts and from 6 (Katz et al., 2016) to 34 participants (Weidenhagen et al., 2008) within the full studies. The most common clinical indication for surgery in the studies was cancer (colorectal, rectal or rectosigmoid) cancer. Other clinical indications for surgery included ulcerative colitis, rectal villous adenoma, ovarian cancer with rectal involvement, familial adenomatous polyposis, diverticular disease, inflammatory bowel disease (table 2). In one study, Endo-SPONGE treatment was indicated for anastomotic leak in the majority of patients but in 3 patients indication for treatment with Endo-SPONGE was for insufficiency of a rectal stump following Hartmann's procedure (Riss et al. 2010).

Across the studies the decision to treat as an inpatient or outpatient and the use of sedation varied and appeared to be based on clinical decision regarding suitability, all Endo-SPONGE treatments were carried out in the secondary care setting (Arezzo et al., 2015; Jimenez-Rodriguez et al. 2018; Kuehn et al., 2016; Mussetto et al. 2017; Nerup et al. 2013; Riss et al., 2009; Rottoli et al. 2018; Strangio et al. 2015; Wasmann et al. 2019). One study (Arezzo et al. 2015) reported that chronic cases were treated in an outpatient setting whereas acute cases were treated initially as an inpatient and discharged to outpatient treatment if conditions were favourable to perform Endo-SPONGE changes in the outpatient setting. Similarly two studies (Jimenez-Rodriguez et al. 2018; Manta et al. 2016) reported all patients were treated initially as inpatients with follow-up treatments performed on an outpatient basis where possible. One study (Strangio et al. 2015) reported that conscious sedation (not general anaesthetic) was used and that outpatient treatment was possible after a few sponge exchanges. Conscious sedation was also used in a second study (Mussetto et al. 2017). One study (Wasmann et al. 2019) reported that sponge changes were done in an

outpatient setting. One study (Nerup et al. 2013) reported that treatment involved an inpatient stay with some patients continuing as outpatients. One study (Rottoli et al. 2018) reported that first application was performed under deep sedation and one study (Riss et al. 2009) reported that treatment was performed under general anaesthesia or moderate sedation and that hospitalisation was only necessary in the case of replacement or poor general condition. One study (Kuehn et al., 2016) reported placement and exchanges of sponges without any sedation or anaesthesia

One UK based study (Srinivasamurthy et al. 2013) recruited 8 patients over a period of 3.5 years. The period of time over which the studies were conducted (1 year to 12 years) and the small number of patients in each study is likely to be reflective of the small number of patients who develop an anastomotic leak following colorectal surgery.

Time to diagnosis of Anastomotic Leak and starting Endo-SPONGE treatment

Eleven studies (Keskin et al. 2015; Kuehn et al. 2016; Milito et al. 2017; Riss et al. 2010; Riss et al. 2010; Rottoli et al. 2018; Srinivasamurthy et al. 2013; Strangio et al. 2015; van Koperan et al. 2009; Wasmann et al. 2019; Weidenhagen et al. 2008) reported the time from surgery to diagnosis of anastomotic leak and 5 studies (Boschetti et al. 2018; Rottoli et al. 2018; Strangio et al. 2015; van Koperan et al. 2009; Wasmann et al. 2019) reported time to treatment with Endo-SPONGE however this varied in whether it was time from surgery to Endo-SPONGE or time from leak diagnosis to Endo-SPONGE. The EAC note that Riss et al. (2010) is a long term follow-up of the same patients included in Riss et al. (2009) and consider that using both studies would be double counting patients for this factor. The EAC has used only Riss et al. (2010) when reporting the values. Time to diagnosis of leak was variably reported as a means or medians but all studies reported a range.

Mean time to diagnosis of leak varied between 6 days to 173 days (Keskin et al. 2015; Kuehn et al. 2016; Weidenhagen et al. 2008). One study (Keskin et al. 2015) reported mean time to diagnosis of leak for early (15 days) and late (173 days) leaks. Median time to diagnosis of anastomotic leak ranged from 9

to 29 days (Milito et al. 2017; Riss et al. 2010; Rottoli et al. 2018; Srinivasamurthy et al. 2013; Strangio et al. 2015; van Koperan et al. 2009; Wasmann et al. 2019). From all studies, time to diagnosis of anastomotic leak ranged from 0 days post-surgery to 343 days post-surgery indicating a wide variation.

One study (Boschetti et al. 2018) reported that Endo-SPONGE treatment started in the month following surgery in 12 cases with a mean delay of 35±56 weeks in the remaining cases. Median time from diagnosis of anastomotic leak to treatment with Endo-SPONGE was 6.5 days (1-158) in one study (Rottoli et al. (2018) and 16 days (0-53) in a second study (Strangio et al. 2015). Two studies reported a median time to treatment with Endo-SPONGE but did not clarify whether it was a time from surgery or a time from leak diagnosis (van Koperan et al. 2009; Wasmann et al. 2019). In one study (van Koperan et al. 2009) 50% of patients started Endo-SPONGE treatment within 6 weeks (median 24 days (13-39) and the remaining patients started treatment after 6 weeks (74 days (43-1,602). One study (Wasmann et al. 2019) reported a median time to Endo-SPONGE treatment of 11 days (IQR 5-15 days).

Neoadjuvant Radiotherapy or Radiochemotherapy

As the main indication for colorectal surgery was cancer, a number of studies reported that patients had received neo-adjuvant radiotherapy or chemoradiotherapy (Arezzo et al. 2015; Boschetti et al. 2018; Kuehn et al. 2016; Milito et al. 2017; Mussetto et al. 2017; Nerup et al. 2013; Riss et al. 2010; Riss et al. 2009; Schiffman et al. 2019; Strangio et al. 2015; Srinivasamurthy et al. 2013; van Koperan et al. 2009; Weidenhagen et al. 2008). One study (Schiffmann et al. 2019) is a comparative cohort study comparing outcomes in patients with anastomotic leak treated with Endo-SPONGE who had received neoadjuvant radiochemotherapy compared with patients who had not received neoadjuvant radiochemotherapy. History of radiotherapy is a risk factor for anastomotic leak but while some information is available relating to outcomes for patients who have radiotherapy or radiochemotherapy, the EAC consider the numbers reported in studies to be too small to provide meaningful subgroup analysis.

Concurrent or additional treatments

Antibiotic use alongside Endo-SPONGE was reported in 6 studies for some patients (Katz et al. 2018; Milito et al. 2017; Riss et al. 2009; Rottoli et al. 2018; Strangio et al. 2015; Weidenhagen et al. 2008).

One study (Wasmann et al. 2019) compared outcomes for patients with anastomotic leak managed conventionally compared with Endo-SPONGE assisted early surgical closure. It should be noted that all patients in this study had undergone ileal pouch anal anastomosis (IPAA) for ulcerative colitis. One clinical expert raised concern as to whether this surgery type may be a contraindication for Endo-SPONGE treatment although it is not listed as such in the Instructions for Use.

One study (Jimenez-Rodriguez et al. 2018) reported that in 10 patients fibrin glue was used in addition after VAC therapy was completed and once the diameter of the cavity was too small to allow entry of the sponge.

The EAC considers that the wide variation reported in the published literature in relation to patient characteristics, time to treatment, concurrent or additional treatments is reflective of the clinical uncertainty and variation in practice. Clinical experts have suggested that the treatment of anastomotic leak does not follow a defined clinical protocol and will largely be dependent on a combination of factors largely determined by patient condition.

4.3 *Results from the evidence base*

Multiple studies report outcomes of interest including overall success rate (21 studies), stoma/ileostomy reversal and/or restoration of bowel continuity (15 studies), number of treatment sessions/sponges (19 studies), treatment duration (15 studies), complications (11 studies), length of hospital stay (3 studies) and quality of life (2 studies). The EAC has presented a pooled result for individual outcomes where possible. The EAC did not apply any formal meta-analysis methodologies (no weighting of studies, no confidence intervals) and the pooled result and ranges are provided as an indication of the variation across studies.

Success Rate

Overall success rate was reported for 18 studies and 3 abstracts (including one comparative study (Schiffmann et al. 2019) and one study in patients with IPAA (Wasmann et al. 2019)). It is important to note that the definition of success varied across the studies. Pooled result from 21 studies was 279/328 (85%) but the range from the individual studies was 40% to 100%.

One study (Schiffmann et al. 2019) compared outcomes in patients who received neo-adjuvant radiochemotherapy with patients who did not. The overall success rate in this study was 94.7% (18/19 patients) with no significant difference observed between patients who received neo-adjuvant radiochemotherapy (10/11) or no neo-adjuvant radiochemotherapy (8/8). In one study with 20 patients (Huisman et al. 2019) surgical closure of the defect was performed after a median of 2 Endo-SPONGE changes in 3 patients with the aim of reducing the duration of Endo-SPONGE therapy. One study (Wasmann et al. 2019) reported a success rate of 100% (18/18) but this was in patients with IAAP which may not be a relevant patient group.

Mortality

All-cause mortality was reported in a total of 10 studies (including one abstract. None of the studies reported mortality associated with Endo-SPONGE treatment specifically. Four studies (Nerup et al. 2013; Schiffmann et al. 2019; Strangio et al. 2015; DiMitri et al. 2010) reported no deaths related to Endo-SPONGE but did not specify whether there were any unrelated deaths. Deaths considered to be unrelated to Endo-SPONGE were reported in six studies. One study (Jimenez-Reodriguez et al. 2018) reported 3 deaths not related to Endo-SPONGE (local recurrence, pneumococcal infection, bowel obstruction secondary to frozen pelvis), one study (Mussetto et al. 2017) reported 2 unrelated deaths (prostate cancer, metastatic cancer), one study (Riss et al. 2009) reported 1 unrelated death (heart attack) and one study (Riss et al 2010) reported 5 unrelated deaths (tumour progression and liver cirrhosis), one study (Keskin et al. 2015) reported 3 unrelated deaths and one study (Huismann et al. 2019) reported 1 unrelated death. Other studies did not explicitly report whether there were any deaths during the study period (related or unrelated).

Stoma reversal and restoration of bowel continuity

Fifteen studies (including one abstract) reported on the reversal of stomas and ileostomies, restoration of bowel continuity and preservation of bowel continuity. Pooled result from 14 studies reporting reversal of stoma or ileostomy was 144/188 (76.59%) but the range from individual studies was 38.5% to 92.3%. One study (Schiffmann et al. 2019) reported the long-term preservation of continuity in patients with and without neo-adjuvant radiochemotherapy; overall preservation of bowel continuity was 63.1% for the whole cohort (63.6% with neo-adjuvant radiochemotherapy and 62.5% without. Time to stoma reversal was reported in 6 studies and varied across the individual studies in terms of when time to reversal assessed and how it was reported. One study (Boschetti et al., 2018) reported stomas were reversed in 85.7% of patients at 6 months while one study (Srinvinvasamurthy et al., 2013) reported that 4/5 stomas were reversed within 6 weeks and 1/5 was reversed after 6 weeks. One study (Huisman et al., 2019) reported a median time from initial surgical resection to stoma reversal of 10 months (3-5). Two studies (Rottoli et al., 2018 & Wasmann et al., 2019) reported a median time to stoma reversal from healing of 2 months (1-6) and 4 months (IQR 3-6) respectively. One study (Weidenhagen et al., 2018) reported that stoma reversal occurred after 168±81.7 days (9-321).

Number of Endo-SPONGE sessions

In total, 19 studies (including 3 abstracts) reported the number or treatment sessions but the number of treatment sessions was variably reported as a mean, a median or a range across individual studies. Across the 19 studies, the number of treatment sessions ranged from 1 to 57 sessions. From 8 studies, the median number of treatment sessions ranged from 3 (1-10) to 8 (1-18) while from 8 studies the mean number of treatment sessions ranged from 2.2 to 18.6 sessions. It is important to note that the individual studies do not always provide a clear definition of a treatment session with some studies reporting a number of sponge insertions/applications (Katz et al. 2018; Keskin et al. 2015; Kuehn et al. 2016; Milito et al. 2017; Rottoli et al. 2018; Srinivasamurthy et al. 2013; Strangio et al. 2015; van Koperan et al. 2019; Wasmann et al. 2019; Martel et al. 2018; McAuley et al. 2013) while other

studies reported the number of treatment sessions (Arezzo et al. 2015; Boschetti et al. 2018; Jimenez Rodriguez et al. 2018; Musetto et al. 2017; Nerup et al. 2013; Weidenhagen et al. 2008 and DiMitri et al. 2010). One study (Schiffman et al. 2019) reported a mean number of sponges of 7.7 for the whole cohort with a mean number of sponges in the neo-adjuvant radiochemotherapy group of 9.6 compared with 5 in the no neo-adjuvant radiochemotherapy group. One study (Wasmann et al. 2019) in patients with IAAP reported a mean 2.7 (SD, 1.4) number of Endo-SPONGE changes per person a mean 3.2 (SD, 1.7) number of sponges used per person.

Duration of treatment

In total, 15 studies (including 1 abstract) reported on the length of treatment (Arezzo et al. 2015; Boschetti et al. 2019; Jiminez-Rodriguez et al. 2018; Kuehn et al 2016; Nerup et al. 2013; Riss et al. 2010; Riss et al. 2009; Rottoli et al 2018; Schiffmann et al 2019; Srinivasamurthy et al 2013; Strangio et al 2015; van Koperan et al 2009; Wasmann et al. 2019; Weidenhagen et al 2008; Martel et al. 2018). Treatment duration was reported as duration of Endo-SPONGE therapy or as time to complete healing across the individual studies. The outcome was variably reported as a mean or median with ranges. One study did not report a total treatment duration but did report length of stay and follow up treatment separately (Nerup 2013). Time to complete healing or closure was reported in 7 studies (Arezzo et al. 2015; Boschetti et al. 2018; Jimenez-Rodriguez et al 2018, Milito et al. 2017; Rottoli et al 2018; van Koperan et al 2009; Wasmann et al. 2019). Median time to complete healing ranged from 40 to 60 days (Arezzo et al. 2015; Milito et al. 2017; Rottoli et al. 2018; van Koperen et al. 2009). Mean time to closure was 10±6.5 (range 2-28) weeks in one study (Boschetti et al. 2019) and 22.3±14.7 days for patients who underwent anterior resection in one study (Jimenez-Rodriguez et al. 2018).

Duration of treatment was reported in (Kuehn et al. 2016; Riss et al. 2009; Schiffmann et al 2019; Srinivasamurthy et al. 2013; Strangio et al. 2015; Weidenhagen et al. 2008; Martel et al. 2018). Median treatment duration ranged between 21 days and 28 days but the number of treatment days ranged from 1 to 109 days (Kuehn et al. 2016; Riss et al. 2009;

Srinivasamurthy et al. 2013; Strangio et al. 2015; Martel et al. 2018). Total treatment duration was 34.4 ± 19.4 days (4-79 days) in one study (Weidenhagen et al. 2008).

One study (Nerup et al. 2013) reported that patients continued treatment for a median 18 days (3-40 days) following a period of inpatient treatment.

One study (Schiffman et al. 2019) reported a significant difference (p=0.04) in mean length of treatment between patients who were treated with radiochemotherapy (31.1 days) compared with patients who had not received radiochemotherapy (15.9 days).

One study (Wasmann et al. 2019) reported a median time to anastomotic closure of 30 days (IQR 17-40 days) in patients with endo-SPONGE assisted closure of anastomotic leak compared with 76 days (IQR 49-339) for patients in whom anastomotic leak was managed without endo-SPONGE (p<0.001).

Complications

Complications were reported in 12 studies (including one abstract). One study (Boschetti et al. 2018) reported a colon perforation in one patient as a result of trying to increase the fistula size to accommodate endo-SPONGE. One study (Huisman et al. 2019) reported chronic sinus in three patients. Three studies (Mussetto et al. 2017, Nerup et al. 2013, Riss et al. 2010) reported stenosis in a total of 4 patients. Two studies (Riss et al. 2010 and van Koperan et al. 2009) reported recurrent symptomatic abscess in a total of 7 patients and one study (van Koperan et al. 2009) reported bleeding in the abscess cavity. One study (Strangio et al. 2015) reported that 1 patient developed ileal fistula and underwent surgical re-intervention. Three studies (Jimenez-Rodriguez et al. 2018, Milito et al. 2017, Wasmann et al. 2019) reported no complications during treatment while one study (Weidenhagen et al. 2008) reported minor bleeding in some patients. In one abstract (DiMitri et al. 2010) one patient experienced arterial bleeding.

Length of stay

Length of hospital stay was reported in three studies (Nerup et al. 2013; Rottoli et al 2018; Weidenhagen et al 2008). Mean length of stay was

30.5±12.8 days in one study (Weidenhagen et al. 2008) while median length of stay was 15.5 days (Rottoli et al. 2018) and 25 days (Nerup et al. 2013). Total length of stay ranged from 6-69 days across all three studies. In a number of studies (Arezzo et al., 2015; Boschetti et al., 2018., Manta et al., 2016; Milito et al., 2017; Riss et al., 2009), length of hospital stay would not be an applicable outcome as patients were treated as outpatients indicating that treatment of anastomotic leaks using Endo-SPONGE might not incur any additional length of stay for patients.

Patient reported outcomes

Patient outcomes were reported in only two studies (Huismann et al. 2019; Riss et al. 2009). Patient acceptability was high with 6/8 patients willing to undergo Endo-SPONGE treatment again if necessary (Riss et al. 2009). Functional bowel outcome was measured using a validated quality of life questionnaire in one study (Huismann et al. 2019). Thirteen patients who had undergone treatment with Endo-SPONGE completed the low anterior resection syndrome score (LARS) questionnaire and results were compared with questionnaires completed by 21 patients who did not have anastomotic leak following surgery. The median LARS score in the Endo-SPONGE group was 37 (23-32) points compared with 30 (4-41) in the comparison group (lower score relates to better quality of life). In the Endo-SPONGE group, three patients (23%) had minor LARS and ten patients (77%) had major LARS and no significant difference in LARS scores was found between the early and late Endo-SPONGE groups ($p = 0.72$).

Table 2: GRADE Quality Assessment

Certainty assessment							Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	
Overall Success Rate (follow up: range 1.5 to 96 months)							
21	observational studies	serious [a,b]	serious [c]	serious [d]	serious [b]	none	⊕◯◯◯ VERY LOW
Stoma/Ileostomy reversal/Bowel continuity restored (follow up: range 1.5 to 96 months)							
15	observational studies	serious [b,e]	not serious	serious [d]	serious [b]	none	⊕◯◯◯ VERY LOW
Number of treatment sessions (follow up: range 2 months to 89 months)							
19	observational studies	serious [b, f]	serious [g]	serious [d]	not serious [h]	none	⊕◯◯◯ VERY LOW
Treatment Duration (follow up: range 1.5 months to 89 months)							
15	observational studies	serious [b, i]	not serious [i]	serious [d]	not serious	none	⊕◯◯◯ VERY LOW
Length of Hospital Stay							
3	observational studies	serious [b, i]	serious [j]	serious [d]	not serious [k]	none	⊕◯◯◯ VERY LOW
Mortality							
10	observational studies	serious [b, i]	not serious	not serious	not serious	none	⊕◯◯◯ VERY LOW
Complications							

Certainty assessment							Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	
11	observational studies	serious [b, i]	not serious	serious [d]	not serious	none	⨁◯◯◯ VERY LOW

Health Related Quality of Life

2	observational studies	serious [b, i]	serious [l]	serious [d]	serious [l]	none	⨁◯◯◯ VERY LOW

Explanations

a. N=21 observational studies (N=16 Non comparative, retrospective case series ; N=1 prospective case series; N=1 non-matched comparative study (not randomised); not reported in two studies and unclear in one whether they are retrospective or prospective).
b. All studies have small sample sizes due to the fact that anastomotic leak is not a common occurrence after colorectal surgery
c. Reported success rate ranged from 56% to 100% however success was defined differently across studies
d. While most of the studies use Endo-SPONGE, without a direct comparator it is difficult to assess the relative effect of Endo-SPONGE compared with standard care
e. Non comparative case series studies, reporting of outcome varies between reporting rate of stoma/ileostomy reversal, time to stoma ileostomy reversal, restoration of bowel continuity, and preservation of bowel continuity
f. The outcome is not clearly defined in the studies. It is not clear whether the number of treatment sessions/exchanges equates to the number of sponges used in each session. Some studies report the number of sponges and not the number of treatment sessions.
g. Number of sessions ranges from 2.2 to 13 across individual studies but these are variably reported as means, medians and counts.
h. It is unlikely that reporting of this outcome is imprecise in individual studies as the number of sessions/exchanges or sponges used is a simple count however care should when comparing this outcome across studies (see inconsistency)
i. Non comparative case series studies
i. Reported time to healing ranged between a median 21 to 60 days. Some studies reported mean time to healing.
j. Reported as a median in two studies and a mean in one study.
k. Unlikely to be imprecise as this is a simple count for length of stay however care should be taken when comparing across studies (see inconsistency)
l. Only two studies report any HRQoL outcomes and they both report differently - one reporting LARS score and one reporting patient satisfaction

Table 3: Outcomes reported by study

Outcome → / Study ↓	Overall success rate	Mortality	Stoma/Ileostomy reversal / Continuity restored	Time to treatment completion	Number of treatment sessions	Complications	Length of hospital stay	Quality of life
Arezzo (2015) Italy (single centre) November 2008 to June 2013	79% (11/14) • 90% (9/10) in acute leaks (<60 days) and 50% (2/4) in chronic leaks (>60 days) (p=0.176). • Success in 100% (8/8) of patients with stoma and 50% (3/6) in patients without it (p=0.055) • Success in 71% (5/7) of patients after radiotherapy and 86% (6/7) among untreated (p=1)	Not reported		Median time to complete healing 40.5 days (8-114)	Median number of treatment sessions 12.5 (range 4-40)		For patients with acute leaks, initial treatment was on an inpatient basis with patients discharged within 1 week to continue treatment as outpatients if appropriate Chronic leaks all treated on an outpatient basis	

Outcome → / Study ↓	Overall success rate	Mortality	Stoma/Ileostomy reversal Continuity restored	Time to treatment completion	Number of treatment sessions	Complications	Length of hospital stay	Quality of life
Boschetti (2018) France (2 centres) January 2013 to December 2016	93% (27/29) success (closure of cavity to <1cm) 24/29 successfully closed at 6 months	Not reported	At 6 months, 85.7% (n=18) of patients presenting with a stoma had closure of stoma	Mean time to treatment to closure 10±6.5 (range 2-28) weeks	Mean number of treatment session was 18.6 ±13 (range 4-57)	1 patient with colon perforation following attempt to increase fistula size to facilitate endo-SPONGE treatment	Not applicable All patients treated on an outpatient basis	
Huisman (2019) Netherlands (2 centres) January 2012 to August 2017	85% (17/20) (reduction of cavity with complete granulation) N=3 patients had planned surgery after a median 2 Endo-SPONGE treatments	0 related to Endo-SPONGE (1 unrelated)	Bowel continuity was restored in 70% (14/20) and stoma reversal occurred in 14/18 (77.8%) of patients Median time from primary resection to stoma reversal was 10 [3–15] months			Chronic sinus developed in 3 (15%) patients who received a definitive stoma.	N/R	Quality of life: 3 patients (23%) had minor LARS, 10 patients (77%) had major LARS.

Outcome → / Study ↓	Overall success rate	Mortality	Stoma/Ileostomy reversal Continuity restored	Time to treatment completion	Number of treatment sessions	Complications	Length of hospital stay	Quality of life
Jiménez Rodríguez (2018) Spain (single centre Study period not reported	91% (20/22) (cavity closure) Full resolution was achieved without further surgery for a total of 19 patients, who were followed- up for a minimum period of 1 year.	0 related to Endo-SPONGE (3 unrelated)	5/13 (38.46%)	Mean time to achieve healing: 22.3 ± 14.7 days; 24.0 ± 15.5 days for the anterior resection group and 19.8 ± 14.09 days for the Hartmann group.	Mean number of endoscopic sessions per patient: 3.1 ± 1.9 in the anterior resection group and 3.2 ± 1.8 in the Hartmann group.	None during procedure n=1 stenosis, n=1 chronic fistula and n=1 osetomylitis	N/R (listed as an outcome)	
Katz (2018) Israel (single centre) May 2014 to December 2016	100% (6/6) (fully recovered) 1 patient treated with endo-SPONGE and antibiotics Sepsis control was achieved following the initial treatment (antibiotics, Endo-SPONGE, and diversion).	Not reported	4/5		Mean number of exchanges: 3.6 (range 3–5 exchanges)		N/R	

Outcome → / Study ↓	Overall success rate	Mortality	Stoma/Ileostomy reversal Continuity restored	Time to treatment completion	Number of treatment sessions	Complications	Length of hospital stay	Quality of life
Keskin (2015) Turkey (single centre) May 2009 to May 2014	80% (12/15) (sufficient granulation)	0 related to Endo-SPONGE (3 unrelated)	10/14		Average number of sponge applications was 2.2 (range, 1 to 5)		N/R	
Kuehn (2016) Germany (single centre) 2007-2015	90% (18/20)	Not reported	15/19	23 days (range 2-109)	Number of sponge insertions 7 (1 - 37) for anastomotic leak population	None reported during procedure.	N/R	

Outcome → / Study ↓	Overall success rate	Mortality	Stoma/Ileostomy reversal Continuity restored	Time to treatment completion	Number of treatment sessions	Complications	Length of hospital stay	Quality of life
Manta (2016) Italy (2 centres) April 2009 to September 2014	100% (7/7) (complete leakage closure with Endo-SPONGE 78% (14/15) closure for OTSC 50% (2/4) with OTSC + stent	Not reported					Not Applicable All patients treated as outpatients	
Milito (2017) Italy (single centre) January 2007 to December 2014		Not reported		Median healing time was 37 days (19-55) Median time of the outpatient therapy was 35 days (16-51)	Between 3-14 sponge exchanges for each patient	No intraoperative complications. No specific side effects during or after the therapy. N=5 had mild anal pain successfully treated medically.	Not Applicable Patients treated as outpatients	

Outcome → / Study ↓	Overall success rate	Mortality	Stoma/Ileostomy reversal Continuity restored	Time to treatment completion	Number of treatment sessions	Complications	Length of hospital stay	Quality of life
Mussetto (2017) Italy (single centre) March 2010 to February 2015	Closure of leakage was achieved in 10/11 (90.9%) (decreased cavity covered with granulation tissue preventing insertion of further sponges)	0 related to Endo-SPONGE (2 unrelated)		Median treatment duration 37 days (18-65 days)	Mean number of treatments was 16 (range 9-23)	During follow-up complications were observed in 2/11 (18%; stenosis in both)	N/R	
Nerup (2013) Denmark (2 centres) February 2008 to 2012	Healing of the perianastomotic abscess cavity was successful in 13/13 (100%) (successful healing)	0 related to Endo-SPONGE	Stoma closure rate was 12/13 (92%)	Median length of stay was 25 days (7-39) and treatment continued for a median 18 days (340 days)	Median number of treatments per patient was 8 (1-18)	Complications 1/13 (7.7%; stenosis treated with surgical intervention)	Median stay 25 days (7-39 days)	

Outcome → / Study ↓	Overall success rate	Mortality	Stoma/Ileostomy reversal / Continuity restored	Time to treatment completion	Number of treatment sessions	Complications	Length of hospital stay	Quality of life
Riss (2010) Austria (six centres) 2009-2009 Indications for endo-SPONGE treatment was AL in 17 patients and rectal stump insufficiency in 3. Results not disaggregated for AL	Long term continued success 15/20 (75%)	0 related to Endo-SPONGE (5 unrelated)	Stoma reversal in 13/17 (76.5%)	Median duration of therapy was 21 days in groups of patients who did or did not develop an abscess		1/20 of patients developed anal stenosis. 5/20 (25%) developed a recurrent symptomatic abscess (3/5 stage C, 1/5 stage B, 1/5 stage A)	N/R	

Outcome → / Study ↓	Overall success rate	Mortality	Stoma/Ileostomy reversal Continuity restored	Time to treatment completion	Number of treatment sessions	Complications	Length of hospital stay	Quality of life
Riss (2009) Austria (single centre) September 2007 to June 2008 3 of 9 patients were suffering from rectal stump failure and only 6 AL. Results not disaggregated for AL.	66.6% (6/9) successful leakage healing (cleaning and shrinking or wound, nearly closed and covered in granulation tissue)	0 related to Endo-SPONGE (1 unrelated)		Median total time of treatment was 3 weeks (2-8) Median duration of Endo-SPONGE replacement was 15 min (5-65)			Not reported in detail – reported as necessary for Endo-SPONGE replacement	Median score for 'patient's satisfaction' was 3 (0-9), 'alteration in daily life activity' was 5 (1-9) and 'pain sensation' 3 (0-6) during the Endo-SPONGE treatment. 6/8 patients would undergo the treatment again, 2/8 would not.

Outcome → / Study ↓	Overall success rate	Mortality	Stoma/Ileostomy reversal Continuity restored	Time to treatment completion	Number of treatment sessions	Complications	Length of hospital stay	Quality of life
Rottoli (2018) Italy (single centre) March 2016 to March 2017	100% (8/8) (cavity reduced in size and covered in granulation tissue)	Not reported	Ileostomy was reversed in 7/8 at a median of 2.5 (1-6) months from the confirmation of healing	complete healing of the leak was documented after a median of 60 (24-90) days from the first treatment	Endo-SPONGE treatment started at a median of 6.5 (1-15) days after diagnosis and lasted for a median of 12 (3-32 days) Device was replaced a median of 3 (1-10) times	No patients reported incontinence to faeces or gas	Median 15.5 days (6-48)	
Schiffmann (2019) Germany (single centre) November 2007 to March 2015	Endo-SPONGE + neoadjuvant radiochemotherapy – 90.9% (10/11 versus Endo-SPONGE only - 100% (8/8) (p=0.381) Success definition not reported	0 related to Endo-SPONGE	Long-term preservation of continuity was 63.6% (7/11) in nRCT group versus 62.5% (5/8) in Endo-Sponge only group (*p*=0.96)	Mean length of treatment was 31.1 days in nRCT group versus 15.9 days in Endo-Sponge only group (p=0.04).	Mean number of sponges 9.6 in nRCT group versus 5 in Endo-Sponge only group (p=0.042)		N/R	

Outcome → / Study ↓	Overall success rate	Mortality	Stoma/Ileostomy reversal – Continuity restored	Time to treatment completion	Number of treatment sessions	Complications	Length of hospital stay	Quality of life
Srinivasamurthy (2013) UK (single centre) September 2007 to May 2011	Closure or reduction achieved in 75% (6/8)	Not reported	Ileostomy reversal in 5/8 (63%). Restoration of bowel continuity within or after 6 weeks of initial surgery in 4/5 (80%) and 1/3 (33%), respectively. Overall 62.5% (5/8).	Median treatment period: 26 days (range 7-49 days)	Median number of sponge applications: 4 (range 1-7)		N/R	
Strangio (2015) Italy (single centre) September 2008 to October 2013	Complete healing in 88% (22/25)	0 related to Endo-SPONGE	Closure of protective ileostomy and restoration of bowel continuity achieved in 11/13 (84.6%) of patients; 2 had definitive stoma	Median duration of 4 weeks (range 1-32)	Median number of applications per patient was 9 (1-39)	1 patient developed ileal fistula and underwent surgical re-intervention.	N/R	

Outcome → / Study ↓	Overall success rate	Mortality	Stoma/Ileostomy reversal Continuity restored	Time to treatment completion	Number of treatment sessions	Complications	Length of hospital stay	Quality of life
Van Koperen (2009) The Netherlands (multicentre) July 2006 to April 2008	Closure of the abscess cavity was successful in 9/16 (56%) patients	Not reported	Stoma reversal in 5/9 patients with closed abscess cavity. 2 on waiting list and 2 with definitive stoma.	Median of 40 days (28-90)	Median number of sponges initially places was 1 (1-3) Median amount of sponge replacements was 13 (8-17)	N=1 had bleeding in abscess cavity, N=1 had stopped treatment due to pain, n=1 stopped treatment due to insufficient cavity closure, n=2 had recurrent abscess	N/R	

Outcome → / Study ↓	Overall success rate	Mortality	Stoma/Ileostomy reversal Continuity restored	Time to treatment completion	Number of treatment sessions	Complications	Length of hospital stay	Quality of life
Wasmann (2019) The Netherlands (single centre) 2002-2017	100% (18/18) at 6 months for ESC group 66.7% (14/21) at 6 months for CM group p=0.01 Cavity clean without significant proximal pouch retraction	Not reported	Median time to stoma reversal was 4 months (IQR 3-6) for ESC group 4 months (IQR 3-13) for CM group P=0.43	Median time to anastomotic closure 30 days (IQR 17-40) for ESC group 76 days (IQR 49 – 339) for CM group p <0.001	Mean number of Endo-SPONGE changes per person was 2.7 (SD 1.4), Number of Endo-SPONGE changes after discharge n=23/48 (47.9%) Mean number of Endo-SPONGE used per person was 3.2 (SD 1.7)	Complications of anastomotic leakage treatment n=0 (0%) in ESC group 2 (9.1%) in CM group	N/R	

Outcome → / Study ↓	Overall success rate	Mortality	Stoma/Ileostomy reversal Continuity restored	Time to treatment completion	Number of treatment sessions	Complications	Length of hospital stay	Quality of life
Weidenhagen (2008) Germany (single centre) 2002-2004	Definitive healing in 96.6% (28/29)	0 related to Endo-SPONGE	Stoma was closed in 22/25. Time to closure was 168.9 ± 81.7 days (9-321 days).	total treatment duration was 34.4 ± 19.4 days (4-79 days)	total number of endoscopic sessions per patient was 11.4 ± 6.3 (1-27) For 25/29 therapy was continued as an ambulatory (outpatient) treatment	No major bleeding occurred, minor bleeding observed in some patients on removal of sponge.	Mean hospital stay 30.5±12.8 (range 10-69)	

Outcome → / Study ↓	Overall success rate	Mortality	Stoma/Ileostomy reversal / Continuity restored	Time to treatment completion	Number of treatment sessions	Complications	Length of hospital stay	Quality of life
DiMitri (2010) *Abstract only* Italy (single centre) January to October 2009	3 pts achieved a significant improvement with cavity reduction <1 cm Symptomatic and leak recurrence in n=2/3 after a mean of 5.5 months form the stoma closure		N=3/3 had stoma closed		N=1 required just one session. n=3 mean 6.3 sessions (range 6-15) and 30.3 days (range 20-50). N=1 stopped treatment after 6 sessions (20 days) due to adverse event	N=1 arterial bleeding	N/R	
Martel (2018) *Abstract only* Northern Ireland (single centre) November 2008 to January 2013	N=4 had definitive closure of cavity			Median duration of treatment was 28.5 days (8-40 days)	Median number of sponge changes 7 (2-11 changes)		N/R	

Outcome → / Study ↓	Overall success rate	Mortality	Stoma/Ileostomy reversal Continuity restored	Time to treatment completion	Number of treatment sessions	Complications	Length of hospital stay	Quality of life
McAuley (2013) *Abstract only* UK (single centre) January 2011 to March 2013	N=2 almost complete cavity closure, n=1 a residual 2.5cm cavity				Mean number of sponge changes 9 (7-12)		N/R	

Abbreviations: AL-Anastomotic Leak; LARS – low anterior resection syndrome score; CM – conventional management; ESC – Endo-Sponge Closure

5 Adverse events

The company submission reports no field safety notices or medical device alerts for this technology. There have been no re-calls and complaints related to Endo-SPONGE are very low.

The EAC searched the MHRA database and identified no adverse events. The EAC noted that the rate of complaints provided by the company appears to have increased in 2019 compared to previous years. The company acknowledge the increase and highlight that none of the complaints were related to clinical use of Endo-SPONGE. The majority of complaints related to packaging or kit content issues. The EAC highlight that although the number of complaints increased in 2019, the number of complaints is extremely low and does not believe that there are any safety concerns at this time.

6 Evidence synthesis and meta-analysis

The company submission included two published systematic reviews with evidence synthesis (Shalaby, 2019 and Popivanov, 2019). In addition, the company included evidence synthesis of data for outcomes not included in the published studies following the methodology used in Popivanov, 2019.

No critical appraisal of the published evidence synthesis has been included in the company submission. The EAC therefore had concerns about using the methods of the Popivanov study to analysis data for additional outcomes.

The EAC appraised both reviews (table 3 and Appendix A) and concluded that Popivanov et al (2019) is a critically low quality review while Shalaby et al (2019) is a low quality review as assessed using AMSTAR (Shea et al 2017). Popivanov et al (2019) aimed to review the literature on endoluminal negative pressure therapy (ENPT) for colorectal anastomotic leak which fits within the scope of this report. The literature search however, was not comprehensive and studies included in the review were not described in any detail in terms of study aims, methodologies or potential risks of bias. Included studies were described as primarily low quality but no details of how quality was assessed were provided. Shalaby et al (2019) aimed to evaluate the safety and efficacy

of EVT in the treatment of anastomotic leakage and rectal stump insufficiency after Hartmann's procedure. The literature search, while more comprehensive than Popivanov et al (2019) was conducted only to July 2017 meaning there is potential for relevant studies to be missed. Quality and risk of bias of the included studies was assessed using appropriate checklists.

A third systematic review (Clifford et al. 2019) was listed in the included studies in the company submission however it was not critically appraised and the outcomes and results were not discussed. Critical appraisal of the review using AMSTAR (Shea et al. 2017) by the EAC indicates that it is a critically low quality review.

The company submission also includes an evidence synthesis of published data for Endo-SPONGE which includes some additional outcomes not reported in the published reviews. The EAC note that the evidence base (published studies) used in the company evidence synthesis is largely the same as that used in the published reviews indicating high level of agreement relating to the evidence base and key studies for this population.

Appendix B of the company submission appears to be an evidence synthesis of current therapies (not including Endo-SPONGE) which the company is using as indirect comparator evidence for Endo-SPONGE. The company submission provides no narrative around the comparator evidence and there are no critical appraisals of the studies used in the comparator analysis. There is no discussion around the limitations or risk of bias of the individual studies. In relation to the evidence synthesis specifically, the company does not address the high degree of heterogeneity as identified by the extremely high I^2 values (67% to 100% for all outcomes apart from stoma reversal rates). The EAC therefore has concerns about the appropriateness of evidence synthesis of this study data without adequate discussion of the individual studies. The EAC also has concerns about the appropriateness of the comparison to other treatment methods, particularly in the absence of any discussion of the limitations of such indirect comparisons.

The company submission does not provide any detail of decisions taken to select data for inclusion from individual studies, particularly the evidence synthesis of comparator studies and as a result the EAC has not been able to validate all of the data in the evidence syntheses.

The EAC note that the company have used a number of the results from their evidence synthesis in the economic analysis and based on the issues highlighted above, the EAC have some concerns about the appropriateness of this. The EAC have provided some pooled results for success rate for non-operative treatment and for stoma reversal as these are key clinical parameters in the economic model (see section 8.3).

Pooled analysis indicates an 85% success rate for Endo-SPONGE but the range from individual studies was 40% to 100%. This compares well with the company evidence synthesis which suggest an 88.8% success rate (weighted mean; 95% CI 85.2 to 92.4; I^2=9%) but again a wide variation across individual studies (56% to 100%).

The company have used percutaneous drainage (PD) as the comparator in their economic model with data based on their pooled analysis of comparator studies. The company submission indicates that non-surgical treatment success rate was 57.4% (weighted mean; 95% CI 41.8 to 72.9%; I^2=77%) however the EAC note that this includes all non-surgical treatments and as the company model is comparing Endo-SPONGE with PD specifically this rate may not be reflective of PD treatment. The EAC attempted to extract data relevant to PD only and note that only 3 studies (Blumetti et al 2014; Damreur et al 2009 and Felder et al 2014) appear to report successful treatment with PD as an outcome however the reporting is not very clear so this is difficult to validate. From these 3 studies (Blumetti et al 2014; Damreur et al 2009 and Felder et al 2014) the rate of success for PD is 70% (the range is 29-82%) which seems closer to the success rate of Endo-SPONGE than the success rates suggested in the company submission. The EAC considers that based on this, treatment with PD may have similar effectiveness to Endo-SPONGE or that while Endo-SPONGE may improve success rates, the degree of improvement may vary.

For stoma reversal rates, the EAC pooled analysis indicated that stoma reversal occurs in approximately 77% of patients (range 38.5% to 100%) when using Endo-SPONGE which again compares favourably with the company analysis which suggests a 79% success rate (weighted mean; 95%CI 71.9 to 86.1; I^2=36%) with a range of 38% to 92%.

For PD the company submission indicates that there is a stoma reversal rate of 62.1% (weighted mean; 95% CI 49.4 to 74.9%; I^2 = 55%) with a range from 50% to 68%. The EAC has been unable to validate all of the data the company have used in their evidence synthesis for this outcome. The EAC report a rate of 82% (50% to 94%) for stoma reversal however this is based on data from only two studies (Harris et al 2010; Sirois-Giguere et al 2013) and one of these studies used trans anal drainage not percutaneous drainage (Sirois-Giguere et al 2013). The addition of data for contained leaks from a third study (Damraeur et al., 2009) gives a rate of stoma reversal of 64% (30% to 94%). In the model the company used a rate of stoma reversal of 54.9% which is the weighted mean rate for stoma reversal for all AL treatment (non-surgical (Byrn et al 2006; Damreur et al. 2009; Harris et al 2010; Sirois-Giguere et al 2013 and surgical management (Khan et al. 2007; Ogilve et al 2012; Thornton et al 2011; Floodeen et al. 2017)). The EAC query whether including the stoma reversal rate for operative treatment is an appropriate reflection of the stoma reversal rate for non-surgical management. When considering the data presented by the company from additional 4 surgical studies (Khan et al. 2007; Ogilve et al 2012; Thornton et al 2011; Floodeen et al. 2017) only, the stoma reversal rate is 52% which is lower than when looking at both non-surgical only (62.1%) and the EAC PD studies only (82%) and is towards the lower end of the range for both suggesting that surgical treatment may result in lower stoma reversal rates. The EAC note that, following additional information from the company, the addition of data on contained leaks from one study (Damraeur et al., 2009) results in a stoma reversal rate of 64% (30%-94%).

The EAC has not conducted a formal meta-analysis as there are no comparative studies available nor has the EAC done any critical appraisal of

the comparator studies used in the company submission. In addition, the EAC was not able to validate some of the data used in the company submission, particularly in relation to the studies used in the comparator evidence synthesis as there was a lack of detail in the company submission around what data were extracted and why. There were also a number of issues and inconsistencies with referencing throughout the company submission, both clinical and economic which made it difficult for the EAC to match data with the correct studies.

Overall, the EAC consider the evidence synthesis is useful in providing an indication the effectiveness of Endo-SPONGE therapy however caution is advised when interpreting the results of the evidence synthesis as it is largely based on very low quality data which will likely reduce the certainty of any estimates.

7 Interpretation of the clinical evidence

Published evidence suggests that indications for primary colorectal surgery is cancer (colorectal, rectal, rectosigmoid) in majority of patients which is supported by clinical expert opinion of what happens in the NHS who indicated that they treated primarily rectal cancer patients. One study was in patients undergoing IPAA for ulcerative colitis suggesting a possible widening of the patient population in whom Endo-SPONGE might be used to treat anastomotic leaks. However, the EAC note that this was not a UK based study, and one clinical expert suggests that IPAA may be a contraindication while a second clinical expert suggests that IPAA would not be a contraindication and the instructions for use for Endo-SPONGE do not list IPAA as a contraindication. The EAC suggest that this should be given consideration in relation to NHS patients.

The EAC assessed the evidence to be very low certainty for all outcomes based on GRADE assessment however the EAC consider that this is a reflection of the fact that the number of patients diagnosed with anastomotic leak following colorectal surgery in the UK is very low.

The published evidence is not clear that Endo-SPONGE would be used as a replacement for antibiotics with six studies indicating that antibiotics were used prior to or alongside Endo-SPONGE. This is supported by information from clinical experts who suggest that antibiotics will be used to control sepsis infection before treating the leak with Endo-SPONGE. One study investigates the use of Endo-SPONGE prior to a planned surgical closure with the aim of achieving an early surgical closure which may indicate a possible option for Endo-SPONGE however this was in patients with IPAA.

The EAC note that use of Endo-SPONGE was associated with both outpatient and/or inpatient treatments and involved general anaesthetic, light sedation or no sedation depending on the patient condition. Again, this is reflective of the experience of NHS clinical experts who suggest that there is no standard approach to sedation and that it will be dependent on the patient.

The EAC highlight that based on the available evidence and clinical expert feedback, there appears to be no ‘typical’ treatment pathway for patients diagnosed with anastomotic leak.

The EAC conclude that Endo-SPONGE may be viewed as an addition to currently available non-surgical treatment options for anastomotic leak prior to surgical interventions with the aim of reducing the need for patients with anastomotic leak to undergo further surgery. The EAC note that the company submission indicates that on the current non-surgical pathway only patients with grade 1 anastomotic leak would be eligible but with Endo-SPONGE a proportion of the more serious grade 2 and grade 3 leaks could also be treated non-surgically. The EAC acknowledge that it is possible that Endo-SPONGE might mean that a proportion of patients become eligible for non-operative treatment using Endo-SPONGE that would otherwise be treated surgically, however one clinical expert reported not using a grading system and just using clinical judgement based on patient condition to determine whether Endo-SPONGE treatment was appropriate. A second clinical expert indicated that when making a clinical decision it is generally binary - patients considered to have a leak or not have a leak. In addition, the EAC note that guidance from the Association of Surgeons of Great Britain and Ireland states

that no consensus on grading system and state that ISREC is over simplistic. Overall the clinical evidence suggests than Endo-SPONGE may successfully treat anastomotic leaks reducing the need for further surgery however the EAC consider the evidence to be very low quality, variable and inconsistent. The EAC acknowledge that based on the small numbers of patients impacted, the quality of the evidence is unlikely to improve over time. The EAC conclude that the decision to use Endo-SPONGE should be made by the treating clinician in discussion with the patient and should consider factors such as severity of leak, patient condition, and patient acceptability.

7.1 *Integration into the NHS*

Information from three clinical experts suggests that the decision to use endo-SPONGE needs to be made by an experience colorectal consultant. One clinical expert suggests that Endo-SPONGE is labour intensive for the surgeon and the patient.

The clinical evidence suggests that the majority of patients require at least one inpatient treatment (initial treatment) and that outpatient follow-up treatment is possible provided the patient is otherwise fit and well. Clinical expert opinion suggests this is also true for the NHS with some patients being treated entirely in the inpatient setting and some patients being treated as outpatients depending on the health and condition of the patient.

The company provides initial training on use of Endo-SPONGE in a group setting such as multi-disciplinary team meetings. No additional or on-going training is required to use the device but the company will provide training if requested.

One clinical expert suggests that the benefits of endo-SPONGE outweigh those of current standard care. They reported that it gave excellent control over sepsis and they were able to discharge patients from the hospital once their health improved following which they were able to have planned definitive surgery. One clinical expert indicated that the benefit of using Endo-SPONGE is likely to be that it might reduce the time to reversal of stomas and improve patient quality of life.

Clinical experts suggest that there needs to be consideration given to Endo-SPONGE treatment being done in endoscopy units and the possible resource implications.

Overall the evidence suggests that integration into the NHS pathway would not require significant changes to current practice.

7.2 *Ongoing studies*

The company submission does not include details of any currently ongoing studies.

The EAC identified 1 study that is currently recruiting. This is an observational patient registry seeking to enrol 100 participants and is due to complete in 2025.

Study	Aim	Location	Design	Intervention	Outcomes	Completion date
NCT02477930	to collect data on the clinical use of endoluminal vacuum (E-Vac) therapy to treat both upper and lower intestinal leaks and perforations	USA	Observational (Patient Registry)	Endo-SPONGE	In-Hospital survival-rate [Time Frame: 6 months]	January 2025

8 Economic evidence

8.1 *Published economic evidence*

Search strategy and selection

The Company did not find any relevant economic studies, but listed 21 studies including outcome and resource data for the Endo-sponge pathway and 30 studies with outcome and resource data for the comparator pathway. The EAC did not find any relevant economic studies.

Published economic evidence review

N/A

Results from the economic evidence

N/A

8.2 *Company de novo cost analysis*

Economic model structure

The Company submitted a model which they described as a budget impact model comprising two separate decisions trees, one for Endo-Sponge and one for a non-surgical comparator which was percutaneous drainage. NICE MTEP methods states that “Given the remit of the programme, the approach expected to be appropriate for most technologies is cost-consequence analysis.” NICE usually produces a resource impact statement and template following positive medical technologies guidance. Furthermore NICE has produced a template for cost consequences models for the MTEP programme. The Company has not given clear justification for their alternative approach. A budget impact analysis is usually used to estimate the likely change in expenditure to a specific budget resulting from the change in intervention for planning purposes, and this can assess affordability, whereas the cost-consequences model is intended to assess value for money. While the submitted model can readily be adapted to calculate a cost per patient, with a 10 year time horizon from the original treatment, the results presented by the company do not reflect this. The company have used the budget impact template to model 100 new patients entering the model for each of the 10 years included, with patients from previous years continuing their stoma

care where relevant. The base-case results presented by the company are for a 1 year time horizon, including costs for the treatment for 100 patients. The submitted base case results can be divided by 100 to give per patient costs for a 1 year time horizon. The EAC was able to use the structure of the Company model as the basis for our modified model and to present results on a cost consequences basis.

Each decision tree in the Company model has 4 branches for grades 1-4 of AL. These lead to either surgical or non-surgical treatment, resulting in AL healed or not healed and final outcome of a permanent stoma or the stoma reversed. Non-surgical treatment is Endo-SPONGE in the treatment decision tree and percutaneous drain in the comparator decision tree. The EAC note that one clinical expert suggests that the grading system is not widely used and that clinically the decision is whether a patient has an anastomotic leak or not. The EAC has adjusted the decision tree to account for this (Figures 1 and 2). This has no impact on the model calculations.

The time horizon of the model is 10 years, although the results submitted were for a 1 year time horizon. Clinical experts have suggested that the indication for colorectal surgery in the majority of patients is rectal cancer. Five year survival for rectal cancer patients is approximately 65% therefore the EAC consider a 10 year time horizon to be appropriate. The perspective is stated to be NHS which is in line with the scope. The model calculations did not include any discounting or take account of survival rates. This would be inappropriate if considering a 10 year model for this population.

The EAC stress tested the model to ensure functionality and while the model largely functions as expected the EAC identified a number of issues (appendix D). In particular the EAC noted that when making changes to some inputs the change may not be carried through the model, as expected.

A small correction was made to calculation of the procedure costs. The model applies the difference in cost between Endo-SPONGE and percutaneous drain procedures to the total number of Endo-SPONGE procedures rather than calculating the cost of each arm individually. This does not account for

the different proportions of surgical and non-surgical procedures in each arm. The EAC corrected this resulting in a small reduction of cost saving (Appendix E). All results reported by the EAC for the company model include this correction.

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Figure 1: Decision Tree for Current Care Pathway

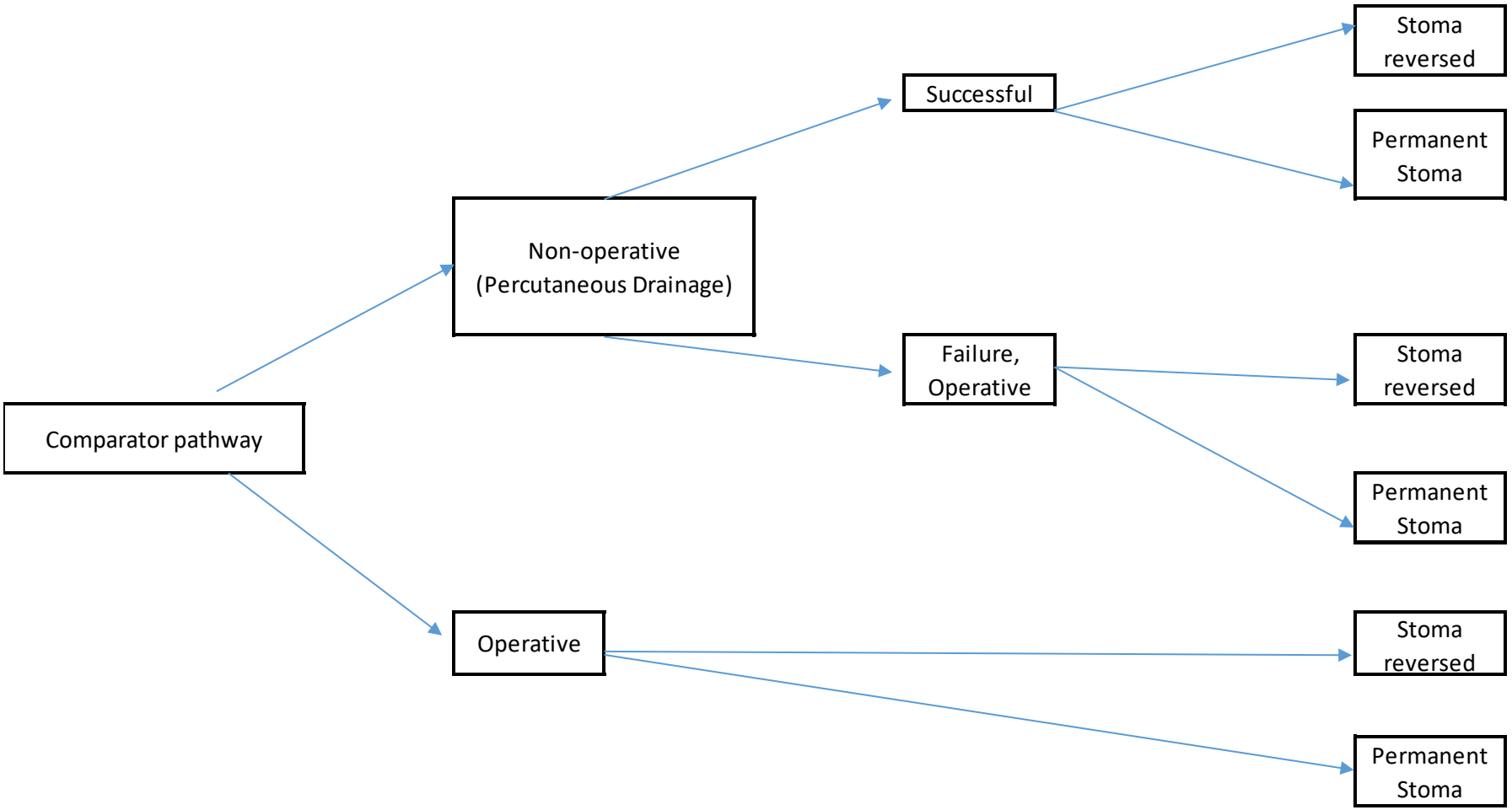
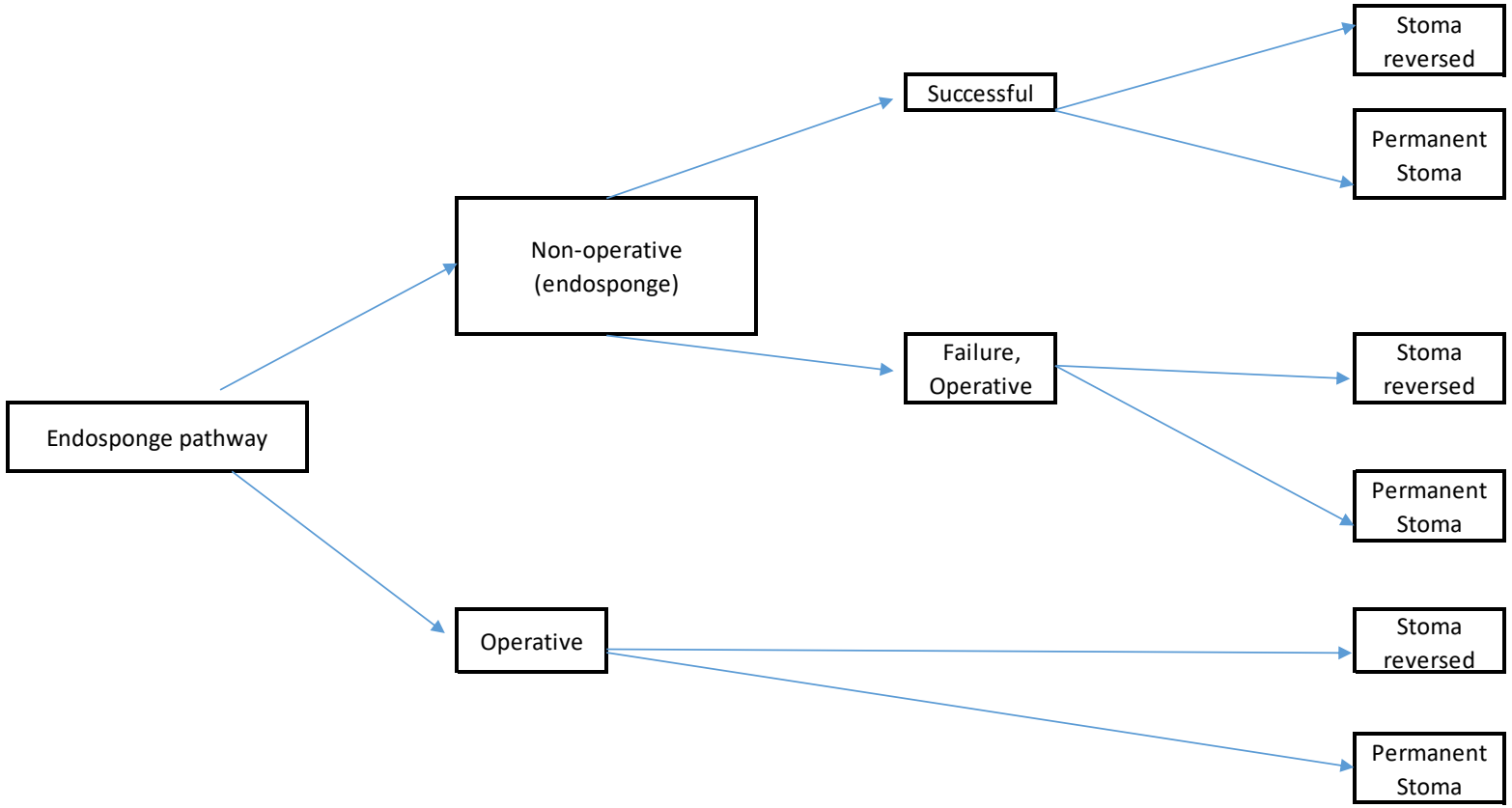


Figure 2: Decision Tree for Endo-SPONGE pathway



8.3 *Assumptions in the company model*

The company have made a number of assumptions around the number of patients with anastomotic leak likely to initially be treated operatively or non-operatively with Endo-SPONGE compared with current non-operative treatment. Additionally, the company have made a number of assumptions around the number of patients who will be unsuccessfully treated non-operatively and will require re-operation. Details of all the assumptions in the model identified by the Company are given in Table 4 below, together with comments from the EAC.

Table 4: Assumptions in Company Submission

Assumption	EAC comment
Proportion of patients with Anastomotic Leak	
Calculations based on 100 AL patients	The number of patients treated by Endo-SPONGE is likely to be much lower in each centre per year. Discussions with clinical experts suggest the rate of anastomotic leak in the UK is quite low therefore the EAC consider it is unlikely that any centre would treat 100 patients per year and consider this to be reflected in the small study sample sizes. The EAC do not consider that the choice of patient number will impact the decision making however highlight that, the results in the company submission should be divided by 100.
40.5% of leaks are grade 1, 32% of leaks are grade 2, 21.5% of leaks are grade 3 and 5.1 % of leaks are grade 4	Information from Asteria *et al.* (2008) (retrospective multicentre study including patients with a new diagnosis of mid or low rectal cancer who underwent sphincter saving surgery). Data is based on low number of patients (n=79) with AL. The EAC note that clinical experts suggest that a grading system is not widely used.
Proportion of patients initially treated non-operatively	

More patients will initially be treated non-operatively in the Endo-SPONGE arm than in the comparator arm	If this assumption is not true, there will be a reduction in the cost-savings due to Endo-SPONGE. The EAC could not validate the company assumption that approximately 27% more patients would be eligible for non-surgical treatment on the Endo-SPONGE pathway. The EAC did not identify any published literature to support or refute the company assumption that more patients would be treated with Endo-SPONGE. It may be reasonable that there would be no difference to the proportion of patients treated non-surgically.
In current AL treatment pathway the company assumed all grade 1 leaks will be treated with non-surgically treatments and all grade, 2,3 and 4 leaks will be treated surgically	Assumption made by the company based on synthesis of data from current pathway (using the weighted mean). The EAC note that clinical experts suggest that a grading system is not routinely used in the UK and treatment of anastomotic leak will largely be dependent on patient condition and clinician decision.
In Endo-SPONGE pathway Assume ALL grade 1 leaks are treated non-operatively. Assume grade 2 and 3 leaks, 50% of leaks are treated non-operatively and 50% are treated operatively. Assume all Grade 4 leaks are treated operatively	Assumption made by the company that Endo-SPONGE will increase the number of patients who will be treated non-operatively. The EAC note that clinical experts suggest that a grading system is not routinely used in the UK and treatment of anastomotic leak will largely be dependent on patient condition and clinician decision. The EAC could not validate the company assumption that approximately 27% more patients would be eligible for non-surgical treatment on the Endo-SPONGE pathway. The EAC suggests that it might be reasonable that there would be no difference to the proportion of patients treated non-surgically.
Healing or re-treatment following non-operative treatment	
ALL leaks failing to heal following non surgical treatment (current pathway or Endo-SPONGE pathway) will require treatment by surgical means	The comparator arm has a greater proportion of leaks failing to heal through non-surgical treatment. The EAC agrees with the assumption that successful treatment with Endo-SPONGE is greater than for percutaneous drainage.
ALL leaks failing to heal following non operative treatment (current pathway or Endo-SPONGE pathway) will require treatment by operative means	Assumption made based on results of evidence synthesis – 11% of patients required additional surgery with Endo-SPONGE. The EAC accept this assumption based on review of the literature but will test this assumption through sensitivity analysis.
Assume out of 100 patients in the current AL pathway 75.433 will require a re-operation	Company assumption based on the assumption that 57.2 patients will have re-operation as an initial solution and 18.23 patients treated non-operatively will require re-operation (total of 75.4 patients overall). The EAC scenarios explore the impact if the proportion of patients treated non-surgically is the same whether with Endo-SPONGE or not, This would result in a reduction in the proportion of patients treated surgically.

Assume out of 100 patients 40.326 in the Endo-SPONGE treatment will require re-operation	Company assumption based on the previous assumption that with the introduction of Endo-SPONGE all grade 1, 50% of grade 2 and 50% of grade 3 leaks will be treated non-operatively. This means that the company assume that a total of 67.75 patients will be treated with Endo-SPONGE initially and 32.25 patients will be treated operatively. Of the patients initially treated with Endo-SPONGE the company assume that 11.2% (n=7.53) will fail and require re-operation. Total re-operations will therefore be 39.78. The EAC assume that 37.2% of patients will be treated surgically initially. As a result, the number of patients treated surgically following an unsuccessful Endo-SPONGE treatment will be lower than for percutaneous drainage.
Number of re-operations saved with Endo-SPONGE versus current AL pathway = 33.352 per 100 patients	Based on the previous information from evidence synthesis. The numbers in EAC scenarios are lower as different assumptions have been made (see table 6).
Stoma reversal following treatment	
Stoma NOT reversed current AL pathway 44.5% of patients	This is based on a meta-analysis of patients who had a successful stoma reversal following either surgical or non-surgical treatment (the company base case uses 45.4% in the model).
Stoma NOT reversed Endo-SPONGE pathway total 29.63 patients out of 100 of patients	This is based on the proportion of patients having surgical treatment plus the proportion of patients having Endo-SPONGE treatment who do not have their stoma reversed. (The company base case calculates 28.88 in the model). Based on the literature, the EAC has assumed that 52% of patients treated surgically and 77% of patients having Endo-SPONGE treatment will have a stoma reversal.
Number of permanent stomas saved with Endo-SPONGE pathway compared with current AL pathway, 18.41 per 100 patients	This is based on the proportion of patients having surgical treatment plus the proportion of patients having non-surgical treatment who do not have their stoma reversed (The company base case calculates 16.52 in the model, see table 6). Based on the literature, the EAC has assumed that of patients treated surgically, 52% and 62% of patients treated non-surgically will have a stoma reversal.
The stoma reversal rate after a surgical operation is the same in both pathways	
Treatment Delivery	

40% of treatments with Endo-SPONGE will be inpatients.	This is a company assumption for which the EAC could find no validation. The EAC note from the literature that in most cases, the first treatment with Endo-SPONGE was on an inpatient basis with subsequent treatments on an outpatient basis where possible. Clinical experts also indicate that patients may be treated entirely as inpatients or may have follow-up treatments on an outpatient basis.
Equipment Requirements	
Each Endo-SPONGE will be connected to one Redyrob bottle.	Based on the communication with the company, EAC learned that up to two sponges can be connected to one bottle. In addition, if more than two sponges are required, a second bottle will be required.

8.4 *Economic model parameters*

The EAC clinical evidence review suggests that there is no 'typical' treatment pathway for a patient diagnosed with anastomotic leak. In particular, decisions relating to antibiotic use, sedation (general or local anaesthetic) or whether patients are treated in an inpatient or outpatient setting appear largely to be driven by clinician or patient preference and are dependent on the condition of the patient.

The EAC approach is to model three possible scenarios based on the available evidence using a number of assumptions to calculate appropriate costs.

Scenario 1 (EAC suggested costing): Endo-SPONGE requires the first treatment to be inpatient, requiring a general anaesthetic and theatre. Subsequent treatments are more minor and can be done in an outpatient type setting.

Information from the clinical experts and from the literature suggests that patients being treated with Endo-SPONGE will have at least one inpatient appointment with general anaesthetic. Following initial application, subsequent Endo-SPONGE changes may be on an outpatient basis with mild sedation. Even where the patient is still an inpatient, the procedure may not require use of theatre facilities or general anaesthesia.

The EAC base case scenario assumes

- that a patient has an investigation for anastomotic leak in theatre, under general anaesthetic with the option to place Endo-SPONGE at the same time
- the costs associated with this would be the Endo-SPONGE equipment costs and 15 minutes of additional theatre time (including staff time)
- all subsequent Endo-SPONGE procedures are carried out as an outpatient appointment **or** if the patient is already an inpatient, Endo-SPONGE procedures are still carried out as a minor procedure in a clinic type setting, and do not require a theatre. In either case the costs are based on outpatient costs.
- costs incurred for all subsequent placement of Endo-SPONGE are the Endo-SPONGE equipment costs plus endoscopy costs for an outpatient setting (using NHS reference costs, which include staff time).
- Inpatients do not occur additional bed days due to Endo-SPONGE, therefore the minor procedure is the only additional cost.
- the same assumptions for settings and costs are used for the comparator arm.

Scenario 2: Endo-SPONGE requires inpatient treatment and GA for the duration of treatment

One clinical expert suggests that patients being treated for anastomotic leak will be patients who are still being treated on an inpatient basis following their primary surgery. Endo-SPONGE treatment would therefore be on an inpatient basis and may require a general anaesthetic for each Endo-SPONGE placement depending on patient condition.

In order to explore the cost impact, the EAC have modelled a scenario where the patient has investigation for anastomotic leak in theatre under general

anaesthetic, with the option to place Endo-SPONGE at the same time and all subsequent Endo-SPONGE placements also require a theatre procedure.

This EAC scenario assumes

- that a patient has an investigation for anastomotic leak in theatre, under general anaesthetic with the option to place Endo-SPONGE at the same time
- the costs associated with this would be the Endo-SPONGE equipment costs and 15 minutes of additional theatre time (including staff time)
- subsequent Endo-SPONGE placements will require a general anaesthetic and theatre time.
- All patients are Inpatients do not occur additional bed days due to Endo-SPONGE. Therefore the procedure is the only additional cost.
- costs incurred for subsequent placement are modelled using the cost of Endo-SPONGE equipment plus day case endoscopy costs (using NHS reference costs, which include staff time)
- the comparator arm is unchanged from EAC Scenario 1

Scenario 3: EAC base-case with percutaneous drainage added

Discussion with clinical experts indicated that there is a possibility that patients will have a percutaneous drain and Endo-SPONGE treatment. To explore the cost impact, the EAC modelled a scenario where the patient has investigation for AL in theatre under general anaesthetic, with the option to place Endo-SPONGE at the same time. A percutaneous drain is also placed at the same time.

The EAC scenario assumes

- that a patient has an investigation for anastomotic leak in theatre, under general anaesthetic with the option to place Endo-SPONGE and percutaneous drainage at the same time

- the costs associated with this would be the Endo-SPONGE equipment costs and 15 minutes of additional theatre time (including staff time) plus the cost of percutaneous drainage and 20 mins of additional theatre time.

- Assumptions and costs for subsequent placements of Endo-SPONGE or percutaneous drain are unchanged from EAC Scenario 1.percutaneous drain will be changed with the same frequency as in the comparator arm.

- the comparator arm is unchanged from EAC Scenario 1

In order to explore the uncertainty around the clinical inputs, the EAC have modelled these three scenarios using the clinical parameters submitted by the company, and alternative parameters based on the EAC interpretation of the data and the possibility that some assumptions may not be correct. These have been modelled for a 1 year and 10 year time horizon.

8.5 *Clinical parameters and variables*

The main clinical parameters included in the company analysis include the number of patients who are treated non-surgically either on the current pathway or with Endo-SPONGE; the number of patients with a successful non-surgical outcome, number of patients who have subsequent surgical repair and the number of patients who have a stoma reversal following non-surgical and/or surgical treatment.

The EAC agree that these are the key clinical parameters for consideration in this patient group but have identified a number of points for discussion in relation to the assumptions made by the company. These clinical inputs have been modelled by the EAC as detailed below, however their remains uncertainty over the most appropriate inputs to use.

There were some discrepancies between the companies values used in the model and in the written submission. Where this is the case, the EAC have taken the values from the written submission as the intended company values.

Proportion of patients treated non-surgically with Endo-SPONGE compared with current non-surgical treatment of leak

Based on published literature, the company assumes that treatment with Endo-SPONGE will mean that 50% of grade 2 and 50% of grade 3 leaks could be treated non-operatively whereas without Endo-SPONGE only patients with grade 1 leaks could be treated non-surgically. In the model, the company assumes this means that 42.8% of patients would be treated non-surgically without Endo-SPONGE and this would increase to 67.2% (67.7% in model) with Endo-SPONGE.

The EAC note that clinical experts suggest that the grading system is not used in a clinical setting and that the decision to treat a patient operatively or non-operatively will depend on the patient condition. The EAC cannot therefore validate the assumption that a proportion of grade 2 and grade 3 leaks would be treated with Endo-SPONGE.

The EAC note that the weighted mean (42.8%) used in the company economic analysis is based on all non-surgical treatment, not just percutaneous drainage which is the comparator in the model. From the company evidence synthesis, the rate of anastomotic leak managed with percutaneous drainage was 62.8% (range 28.5 to 100%). The EAC also note that one study reports that 73% of anastomotic leaks were managed non-surgically without Endo-SPONGE (Blumetti et al. 2014).

Based on the available evidence and clinical expert feedback, the EAC cannot validate the assumption that Endo-SPONGE would result in an increase of 27% of patients eligible for non-surgical treatment as proposed by the company. The EAC have therefore assumed that the proportion of patients treated with Endo-SPONGE is the same as for other non-surgical treatments. The EAC note that if the introduction of Endo-SPONGE does increase the proportion of patients routed to non-surgical treatment, there would be an increase in cost savings.

Success rates for non-surgical treatment

The company submission suggests that the anastomosis healing rate is 88.8% (weighted mean) for Endo-SPONGE with a range across studies of

56% to 100%. EAC pooled analysis indicates an 85% success rate for Endo-SPONGE but the range from individual studies was 40% to 100%. This compares well with the company evidence synthesis. The EAC therefore consider that a high success rate with Endo-SPONGE is a valid assumption but notes the variation reported across the individual studies.

The EAC note that although the company model includes percutaneous drainage as the comparator, the success rate of 57.4% used in the model is a success rate for all non-surgical treatments. The EAC note that successful treatment with PD as an outcome is not clearly reported but pooled data from 3 studies (Blumetti et al., 2014; Damraeur et al., 2009; Felder et al., 2014;) the rate of success for PD is 70% (the range is 29-82%). The EAC therefore model an assumption that 70% of PD treatments are successful. If treatment with PD is not as successful as with Endo-SPONGE, the cost savings will increase.

Proportion of patients who have a stoma reversal

The company have assumed that 45.4 % of patients in the current pathway will not have their stoma reversed compared with 28.8% of patients in the Endo-SPONGE pathway. The EAC note that these assumptions include the patients who have stoma reversal following surgical treatment initially plus patients who have stoma reversal following non-surgical treatment.

When considering the patients treated non-surgically only using Endo-SPONGE, the EAC pooled analysis indicated that stoma reversal occurs in approximately 77% of patients (range 38.5% to 100%) following treatment with Endo-SPONGE which again is similar to the company analysis (79% weighted mean). For stoma reversal following current non-surgical treatment however, the EAC were unable to validate the data used by the company to calculate a weighted mean of 62.1%. The EAC report a rate of 82% (50% to 94%) for stoma reversal following percutaneous drainage however this is based on data from only two studies. As this is based on only two studies the EAC modelling of clinical inputs uses the same rate of stoma reversal following non-surgical treatment as the company submission (62%).

In their submission, the company used a rate of stoma reversal of 54.5% (weighted mean rate for stoma reversal for all AL treatment (non-operative and operative)) for patients following surgical treatment in both arms (54.6% in model). The EAC note that when considering the 4 additional studies in the company evidence synthesis (Khan et al. 2007; Oglive et al. 2012; Thornton et al. 2011 and Flooden et al 2015) the stoma reversal rate is 52% which compares well with the company assumption.

The EAC modelling of clinical parameters therefore assumes that the rate of successful stoma reversal following non-surgical treatment is 77% for Endo-SPONGE and 62% for PD and 52% for stoma reversal following surgical treatment of anastomotic leaks.

The EAC acknowledge that there are difficulties with validating assumptions around the number of patients treated non-surgically and surgically on each pathway as well as the number of patients who require a re-operation due to failed non-surgical treatments. Clinical experts have confirmed that there is no standard pathway for patients in terms of their treatment with the decision on whether to treat surgically or non-surgically being based on the condition of the patient. The EAC agree with the assumption that treatment with Endo-SPONGE might reduce the number of patients who have a subsequent re-operation and that patients treated with Endo-SPONGE are more likely to have their stoma reversed compared with current treatment however remain aware that the literature is poor.

Proportion of patients who fail non-surgical treatment and have subsequent surgical treatment

The company assume (based on results of their evidence synthesis) that 100% of patients who fail with non-surgical treatment will go on to operative treatment. The EAC considers this to be a valid assumption but notes that if some patients do not require an operation, but are managed conservatively, there may be a reduction in the cost saving due to Endo-SPONGE.

The company have assumed that based on the total number of patients on the current pathway who have re-operation (including patients who have re-operation following failed non-surgical treatment), the number of re-operations

saved with Endo-SPONGE is approximately 33.5 per 100 patients (difference between re-operations with current non-operative (75.4) and re-operations with Endo-SPONGE (39.9). The EAC note that this difference is reliant on earlier assumptions around the number of patients having re-operations on each pathway being accurate. If, for example the proportion of patients being treated non-surgically is the same whether Endo-SPONGE is used or not, the number of patients who have surgical treatment initially also be the same and the cost savings associated with Endo-SPONGE will be reduced accordingly. . This is explored in the EAC scenarios.

Table 5: Clinical parameters used in the company's model and any changes made by the EAC

Variable	Company value	Source	EAC value	EAC comment
Anastomotic leaks non-operatively on the current pathway	42.8%	Company evidence synthesis	62.8%	The EAC cannot validate the assumption that Endo-SPONGE would result in an increase of 27% of patients eligible for non-surgical treatment as proposed by the company.
Anastomotic leaks treated non-operatively with Endo-SPONGE	67.2% in submission, 67.7% in model	Company evidence synthesis	62.8%	
Successful non-operative on the current pathway	56.6% in submission, 57.4% in model	Company evidence synthesis	70%	Successful treatment with PD as an outcome is not clearly reported but from 3 studies the rate of success for PD is 70% (the range is 29-82%).
Successful non-operative with Endo-SPONGE	88.8%	Company evidence synthesis	85%	Result from EAC pooled analysis (range 40% to 100%)

Surgery for failed non-operative on current pathway	100%	Company evidence synthesis	100%	
Surgery for failed non-operative with Endo-SPONGE	100%	Company evidence synthesis	100%	
Stoma reversal on current pathway	54.5% in submission, 54.6% in model	Company evidence synthesis	62%	Results from literature (see section 9.4)
Stoma reversal with Endo-SPONGE	79.0%	Company evidence synthesis	77%	Result from EAC pooled analysis (see section 9.4)
Stoma reversal with surgical treatment	54.5% in submission, 54.6% in model	Company evidence synthesis	52%	Results from literature (see section 9.4)

The effect of the EAC changes are summarised in table 6 and further details of EAC changes to the model are in Appendix E. In the model submitted by the company, for every 100 patients treated the introduction of Endo-SPONGE would avoid 35 re-operations and 15 permanent stomas. When the EAC modelled the alternative clinical inputs, this was reduced to 9 re-operations and 9 permanent stomas avoided per 100 patients.

Table 6: Re-operations and stomas avoided as modelled by company and EAC at 1 year, per 100 patients

Per 100 patients in model, at 1 year	Company's submitted model			EAC clinical inputs		
	Endo-SPONGE	Percutaneous Drainage	Operations	Endo-SPONGE	Percutaneous Drainage	Operations
Patients receiving initial operative treatment	32.3	57.2	24.9	37.2	37.2	0

Patients receiving operative treatment subsequent to non-operative failure	7.6	18.2	10.7	9.4	18.8	9.4
Total re-operations	39.9	75.4	**35.6**	46.6	56.0	**9.4**
Total stomas	28.9	45.4	**16.5**	32.3	41.7	**9.4**

Resource identification, measurement and valuation

The company has used a number of different costs and sources in their model. The EAC have checked and validated the sources (Table 7) and made corrections or adjustments where necessary.

The EAC note that the company submission has broken down the cost of treatment into the various component parts (staff costs, theatre costs, equipment costs etc.) and while most costs could be validated, there were some costs which could not.

Table 7: Cost parameters used in the company's model and changes made by the EAC

Parameter	Company value	EAC value	Source
Staff time, per hour			
Nurse, band 5	£37.00	NA	PSSRU 2018
Nurse, band 6	£45.00	NA	PSSRU 2018
Nurse average	£41.00	NA	Mean (not weighted)
Theatre Support , band 2	£22.00	NA	PSSRU 2018
Anaesthetist, Registrar	£43.00	NA	PSSRU 2018
Anaesthetist, Associate specialist	£105.00	NA	PSSRU 2018
Anaesthetist, Consultant	£108.00	NA	PSSRU 2018
Anaesthetist AVERAGE	£85.33	NA	Mean (not weighted)
Radiologist, Registrar	£43.00	NA	PSSRU 2018
Radiologist, Associate specialist	£105.00	NA	PSSRU 2018
Radiologist, Consultant	£108.00	NA	PSSRU 2018
Radiologist average	£85.33	NA	Mean (not weighted)
Consultant Colorectal Surgeon	£108.00	NA	PSSRU 2018
Facilities			
Chest x-ray	£25	NA	Based on a FOI request stating Chest X-ray tariff, 2014
Xray department, per hour	£300.00	NA	Assumes equivalent to 12 Chest x-rays
Endoscopy unit, per treatment	£94.30	NA	Unknown : Original link not accessible, company provided link to 2001 BSG Working party report, but relevant information could not be identified by EAC

Theatres	£1,200.00	£1,201.00	Company: NHS Institute for Innovation and Improvement "Improving quality and efficiency in the operating theatre", 2009 (No inflation applied) EAC: ISD Scotland cost book 2019, average hourly cost for theatres (acute sector)
Bed days	£413	NA	Company: NHS Wales 2011/12.
Duration of procedures			
Surgery (hours)	4.5	3.95	Company: NHS Improvement, Operating theatres: opportunities to reduce waiting lists (2019) EAC: Ramsay 2012
Endo-SPONGE insertion (min)	15	unchanged	Company: (Arezzo et al. 2015b) (Riss et al. 2009)
Percutaneous drain insertion (min)	20	unchanged	On request company provided a patient information leaflet stating that the procedure may be over in 20 minutes
Number of procedures			
Endo-SPONGE procedures	10.7	unchanged	Company submission, meta-analysis (p.100)
Percutaneous drain procedures	4.4	unchanged	Harris et al. 2012 (5 patients)
Equipment costs			
Endo-SPONGE sponge	£250.24	unchanged	Company submission
Redyrob bottle	£20.87	unchanged	Company submission
Percutaneous drain and bottle	[redacted]	unchanged	Company submission
Other costs, ongoing care			
Stoma care (annual)	[redacted]	unchanged	Company submission, based on multiple sources
Alternative stoma care cost (EAC)		££2896.96	Tillin et al (2005) inflated to 2018/9 costs

Staff costs:

The company have used PSSRU tables for staff costs, which is an appropriate source, however these are used in addition to procedure costs that already include staff time. Therefore the EAC has not used any of these costs in their base model.

Equipment costs:
The company have used their list price of £2502.39 for a pack of 10 Endo-SPONGE sponges, and a cost of £208.72 for 10 Redyrob bottle (required for each Endo-SPONGE procedure). The company have used a mean cost of [redacted] for the percutaneous drain and bottle derived from 95 items taken from NHS Supply chain. The EAC accept these costs.

Stoma care costs:
The company have calculated an annual cost of stoma care by taking costs from Prescriber cost analysis (PCA) and Dispensing Applying Contractor (DAC) information obtained from NHS Business Services. The total spend for 6 months is used to estimate an annual spend, this is then divided by the estimated number of people with stomas to give a per patient cost. The EAC is unable to access the source material for the costs, although large amounts of data are included in separate spreadsheets of the model. The costs appear to include disposable items for stoma care such as adhesive rings, adhesive remover, bag covers, belts, solidifying agents, filters and dressings. It also includes appliance use reviews, professional fees and stoma customisation fees. From information the EAC have accessed from the NHS Business Services, the items with calculated prices are chosen from a much wider list, and there is no narrative explanation of the rationale for this. In addition the spreadsheet of “Tableau data” is provided by Inspiremed, and the EAC have no additional information on how this was calculated, but it appears to include stoma plates and bags.

The company have considered a large number of costs from appropriate data sources to compile the annual cost of stoma care of [redacted], however the EAC are not able to verify the accuracy or completeness of this costing.

Alternative sources for annual stoma care costs include economic analysis included in a HTA reporting outcomes of electrically stimulated gracilis neosphincter surgery (Tillin, 2005) which stated a cost of £2125 (2005). This includes follow-up visits, GP visits, medications and stoma appliances. The EAC has inflated to £2896.96 for 2018/19 costs, and used this in the sensitivity analysis.

Procedure costs

For each of the three main procedures modelled (Endo-SPONGE insertion, percutaneous drainage insertion, and surgical repair) the company have taken an hourly cost for the facilities and staff required and multiplied these by the estimated time requirement. The cost of equipment specific to Endo-SPONGE or percutaneous drainage has then been added. The EAC consider that the facilities costs used all include staff time already, and have therefore proposed alternative costing mechanisms, which are detailed below in tables 8 – 10.

The Endo-SPONGE procedure is costed by the company as using an endoscopy unit, with a cost of £94.30 per procedure. The company quote "Approximately 530,000 endoscopies are performed each year at a cost to the NHS of £50 million". Regardless of the source or accuracy of this statement, the cost of an endoscopy is assumed to include staff time.

The percutaneous drainage procedure is costed by the company as requiring interventional radiology facilities. The cost for these facilities is based on a cost of £25 per chest x-ray, estimated at 5 minutes duration. This has been extrapolated to give a cost of £300 per hour in the submitted model. A chest x-ray and interventional radiology placement of a percutaneous drain are not comparable procedures, the source is poorly referenced, and as a tariff it is likely to have included the cost of staffing in the original price.

Theatre costs used by the company are based on an NHS Institute for Innovation and Improvement document "Improving quality and efficiency in the operating theatre" published in 2009, which states "Running costs for an operating theatre average approximately £1,200 per hour". No additional information is given in this document to indicate which costs are included as running costs, or what the source of this data is, no inflation has been applied to the cost. The EAC has investigated other possible sources of theatre costs. ISD Scotland publish detailed costs in their annual Cost Book. Table SFR 5.10_2019 lists the total expenditure including direct staff costs, supply costs and allocated costs, together with the total theatre hours per year. This gives

an average theatre cost of £1201, for hospitals in the acute sector, although there is a wide variation between the different providers.

The NICE guidance update for Colorectal Cancer (NG151) adopted this method based on Ramsay 2012 (HTA Systematic review and economic modelling of the relative clinical benefit and cost-effectiveness of laparoscopic surgery and robotic surgery for removal of the prostate in men with localised prostate cancer).

The time for the surgical procedure is based on a statement from NHS Improvement that 4 hours was the most commonly planned duration for a scheduled theatre session (for any procedure). There is no explanation given for the use of 4.5 hours. The EAC identified a mean procedure length for laparoscopic surgery to treat localised prostate cancer of 237 minutes, or 3.95 hours (Ramsay 2012) that was also used in the NICE guidance update for Colorectal Cancer (NG151).

The procedure costs include an additional 14.18 bed days. This is based on the difference in the company's evidence synthesis between patients with AL and those without. There is no justification given for using this data to model the different length of stay for patients with AL who are treated operatively and those who are treated non-operatively. The cost for the ward bed-days is based on the NHS Wales Delivery plan for the critically ill (2013). A more appropriate approach would have been to take the NHS Reference excess bed day costs for Complex and Very complex large intestine procedures (FF30A-FF31D), which gives a weighted mean of £335 per day (NHS Reference costs 2017-18). The EAC have not explored this further as our preferred approach does not include additional bed day costs.

Table 8: Endo-SPONGE placement

Endo-SPONGE placement procedures		
Company submission for all Endo-SPONGE placements		
Endoscopy unit (for 15 minutes)	£94.30	PSSRU 2018
Consultant (for 15 minutes)	£27.00	PSSRU 2018
Nurse (for 15 minutes)	£10.25	PSSRU 2018
Endo-SPONGE sponge	£250.24	Company submission
Redyrob bottle	£20.87	Company submission
Procedure total	**£402.66**	
EAC alternative for initial placement, assuming during an investigative procedure in theatre		

Theatre time, including staff (15 min)	300.25	ISD Scotland Cost Book, 2019
Endo-SPONGE sponge	£250.24	Company submission
Redyrob bottle	£20.87	Company submission
Procedure total	**£571.36**	
EAC alternative for subsequent placement, assuming outpatient clinic setting		
Procedure	£199.74	NHS Reference costs, 2018/19, FE01Z, FE02Z, FE30Z, FE40Z, FF31D, FF33B, FF34C, FF36Z, FF41C, FF42Z, gen surgery, col. Surgery, gastroenterology, outpatients. Weighted average
Endo-SPONGE sponge	£250.24	Company submission
Redyrob bottle	£20.87	Company submission
Procedure total	**£470.85**	

Table 9: Percutaneous Drain placement

Percutaneous drain placement procedures		
Company submission for all Percutaneous drainage placement		
X-ray dept (15 min)	£99.00	PSSRU 2018
Radiologist (15 min)	£28.16	PSSRU 2018
Nurse (15 min)	£13.53	PSSRU 2018
Percutaneous drain and bottle	[redacted]	Company submission
Procedure total	**£182.95**	
EAC alternative for initial placement, assuming during an investigative procedure in theatre		
Theatre time, including staff (20 min)	£400.33	ISD Scotland Cost Book, 2019
Percutaneous drain and bottle	[redacted]	Company submission
Procedure total	**£442.59**	
EAC alternative for subsequent placement, assuming outpatient clinic setting		
Procedure	£291.05	NHS Ref costs 2018/19, outpatients FF51E, FF53A, YF04C, Interventional radiology
Percutaneous drain and bottle	[redacted]	Company submission
Procedure total	**£333.31**	

Table 10: Surgery costs

Surgical repair procedures		
Company submission for all repeat surgical repair		
Theatre (4.5 hours)	£5,400.00	
Surgeon (4.5 hours)	£486.00	PSSRU 2018
Anaesthetist (4.5 hours)	£384.00	PSSRU 2018
Scrub nurse (2 x 4.5 hours)	£369.00	PSSRU 2018
Theatre support (4.5 hours)	£99.00	PSSRU 2018
14.18 bed days	£5,856.34	
Procedure total	**£12,594.34**	
EAC alternative for repeat surgical repair (1)		
Theatre time, including staff (3.95 hours)	£4,743.95	ISD Scotland 2019 average hourly theatre cost.
No additional stay, already inpatient	£0	
Procedure total	£4,743.95	
EAC alternative for repeat surgical repair (2)		

Surgical procedure (includes 7 days additional stay)	£8,523.68	NHS Ref costs 2018-19, weighted average, elective inpatient stay. FF30x, FF31x, FF32x, FF33x, FF34x.
Procedure total	**£8,523.68**	

Time horizon

The EAC modelling included adaptation to give results at 10 years for 1 patient, including the use of 3.5% discounting and mortality. The mortality information used was for patients with bowel cancer, and taken from Cancer Research UK.

8.6 *Sensitivity analysis*

Based on the variation observed in the published literature, the EAC disagrees with the company approach to sensitivity analysis where the individual parameters are varied by only +/-10%. The EAC have used the EAC base case (Scenario 1) and modelled the uncertainty reflected in the literature and by the clinical experts. Some parameters are modelled with a wide variance, for example, the number of sponges (equivalent in model to the number of treatment sessions), or the costs of procedures that could be carried out in clinics or theatres. Results from the economic modelling

Base case results

In the Company model the cost per treatment for Endo-SPONGE (£402.66) is greater than for percutaneous drainage (£182.95), and there are more treatments required per course for Endo-SPONGE (10.7) compared with percutaneous drainage (4.4). The resulting the overall cost per course of treatment is higher for Endo-SPONGE (£4,308.46) than for percutaneous drainage (£804.98). The cost saving in the Company model is due to fewer patients in the Endo-SPONGE branch requiring re-operation and consequent stay in hospital, which the company costed at £12,594.34 per patient. Furthermore the Company model includes a cost saving for the increased number of Endo-sponge patients who avoid a permanent stoma. This is calculated as an annual cost, however the results are reported for the first year only. There was no validation of the model as the Company did not gain access to external clinical experts.

The company submission estimates a cost saving of £2,419.51 per patient in year one with Endo-SPONGE.

The EAC made a number of changes to the clinical and cost assumptions in the company submission (tables 5 - 10) which impacted the overall costs of Endo-SPONGE and comparator treatment.

Using the EAC costs and the company's clinical inputs for Scenario 1a, Endo-SPONGE is cost saving by ££725.94 in year 1. If the EAC alternative clinical inputs are used, then Endo-SPONGE incurs a cost of £1,141.10 in year 1 compared with percutaneous drainage (Scenario 1b).

When modelling the cost-savings over a 10 year time horizon, using the EAC costs (table 13), Endo-SPONGE becomes cost saving using either set of clinical inputs (£2,829.34 for company inputs, £68.22 for EAC alternatives). The company did not model a 10 year time horizon therefore the EAC cannot comment on any difference in cost estimates.

The EAC alternative scenarios both result in Endo-SPONGE becoming more costly than the submitted model or EAC Scenario1. In scenario 2 (table 13) Endo-SPONGE is cost incurring by £2,792.13(Company inputs) or £4,427.34 (EAC inputs) per patient in year 1 compared with percutaneous drainage. This is due to the additional theatre costs for Endo-SPONGE applications. In scenario 3 which assumes that patients get both Endo-SPONGE and percutaneous drainage, Endo-SPONGE is cost saving by £1,770.37 with the company clinical inputs, but cost incurring by £2,130.73 using the EAC alternative inputs. This is due to the additional cost of patients receiving both percutaneous drainage and Endo-SPONGE in the Endo-SPONGE arm. The company cost savings are largely driven by the assumption that treatment with Endo-SPONGE will reduce the number of re-operations and increase the number of stoma reversals in this patient group, compared to percutaneous drainage. The EAC clinical inputs represent a more conservative assessment of the cost of Endo-SPONGE treatment compared with percutaneous drainage that the company submission. The EAC consider that the uncertainty around the clinical evidence and the lack of a standard approach to treating

patients with anastomotic leak mean it is important to consider the possibility that Endo-SPONGE does not reduce the number of re-operations or increase the number of stoma reversals by as much as the company submission suggests.

Table 11: Summary of alternative results for 1 year time horizon

	Company's results, corrected for 1 patient			EAC results (Scenario 1, alternative clinical inuts)		
	Endo-SPONGE	**Percutaneous Drainage**	**Cost saving per patient**	**Endo-SPONGE**	**Percutaneous Drainage**	**Cost saving per patient**
Device	£2,916.83	£344.53	-£2,572.30	£3,227.05	£989.63	-£2,237.42
Reoperation	£5,022.93	£9,500.26	£4,477.33	£3,973.74	£4,776.67	£802.93
Permanent Stoma Cost (per year)	£899.50	£1,413.98	£514.48	£1,005.98	£1,299.37	£293.39
Total	**£8,839.26**	**£11,258.77**	**£2,419.51**	**£8,206.77**	**£7,065.67**	**-£1,141.10**

Table 12: Summary of Clinical inputs used in economic model versions

	Base case model	Written submission (EAC Scenarios 1a, 2a, 3a)	EAC alternative clinical inputs (EAC Scenarios 1b, 2b, 3b)
Clinical inputs used			
% treated non-operatively: Comparator	42.8%	42.8%	62.8%
% treated non-operatively: Endo-SPONGE	67.7%	67.2%	62.8%
Probability of non-operative success: Comparator	55.6%	57.4%	70%
Probability of non-operative success: Endo-SPONGE	88.8%	88.8%	85%
Probability of stoma reversal: Comparator	54.6%	54.5%	62%
Probability of stoma reversal: Endo-SPONGE	79.0%	79.0%	77%
Resulting impact on patients			
Total operations avoided using Endo-SPONGE	**35.6**	**35.1**	**9.4**
Total stomas avoided using Endo-SPONGE	**16.5**	**16.4**	**9.4**

Table 13: EAC Results for Scenario Analysis

Alternative Scenarios modelled	Endo-SPONGE	Percutaneous Drainage	Cost saving per patient
1 year time horizon, no discounting			
Company submitted model, 1 patient, at 1 year	**£8,839.26**	**£11,258.77**	**£2,419.51**
Based on company written submission, 1 patient, at 1 year	£8,877.44	£11,258.78	-£2,381.34
Using clinical inputs from written submission			
EAC Scenario 1a: 1st procedure in theatre, subsequently in clinic.	£7,793.75	£8,518.10	**£724.35**
EAC Scenario 2a: All Endo-SPONGE procedures in theatre	£11,310.23	£8,518.10	-£2,792.13
EAC Scenario 3a: As Scenario 1, but all Endo-SPONGE patients also get Percutaneous Drainage	£8,852.72	£8,518.10	-£334.62
Using alternative EAC inputs			
EAC Scenario 1b: 1st procedure in theatre, subsequently in clinic.	**£8,206.77**	**£7,065.67**	**-£1,141.10**
EAC Scenario 2b: All Endo-SPONGE procedures in theatre	£11,493.01	£7,065.67	-£4,427.34
EAC Scenario 3b: As Scenario 1, but all Endo-SPONGE patients also get Percutaneous Drainage	£9,196.41	£7,065.67	-£2,130.73
10 year time horizon, 3.5% discounting, mortality included			
Using clinical inputs from written submission			
EAC Scenario 1a	**£11,517.12**	**£14,346.46**	**£2,829.34**
EAC Scenario 2a	£15,033.60	£14,346.46	-£687.14
EAC Scenario 3a	£12,576.09	£14,346.46	£1,770.37
Using alternative EAC inputs			
EAC Scenario 1b	**£12,353.39**	**£12,421.61**	**£68.22**
EAC Scenario 2b	£15,639.62	£12,421.61	-£3,218.02
EAC Scenario 3b	£13,343.02	£12,421.61	-£921.41

Sensitivity analysis results

The Company's sensitivity analysis comprises a simple univariate analysis whereby each variable identified as having an impact on the model is varied +/- 10%.

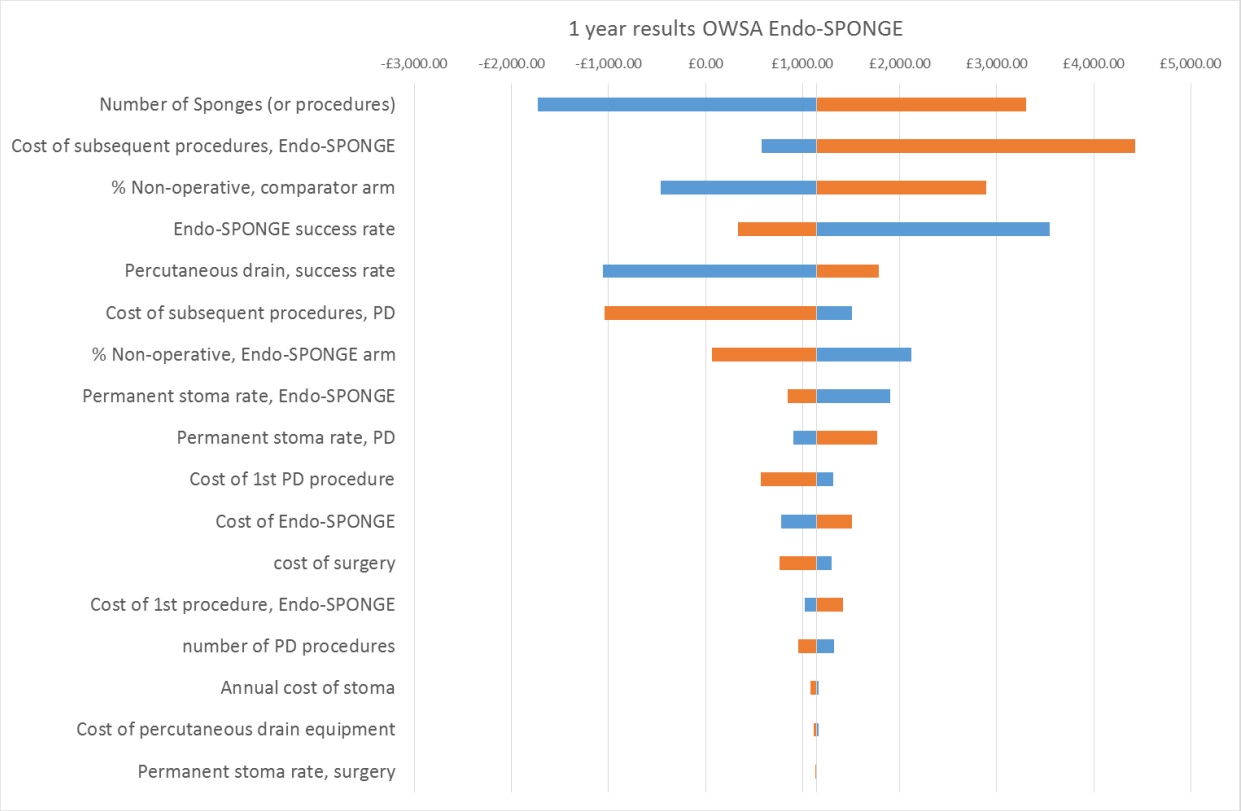
For the 3 variables identified by the company as having the greatest impact, a multi-variate sensitivity analysis involved changing all 3 variables simultaneously by +10% or -10% in a favourable or unfavourable direction,

and then by +/-25%. There was no probabilistic sensitivity analysis. The Company concluded the model was very robust.

The EAC considered the sensitivity analysis to be inadequate given the considerable variability between patients and uncertainty in the values of parameters. One clinical adviser have described the Endo-SPONGE procedure as labour intensive. For example, although some cases may take 15 minutes in theatre, others take longer. Based on EAC contact with clinical advisers, 15 minutes should be considered a minimum theatre time.

The company sensitivity analysis results should all be divided by 100 to give a per-patient cost, and are reported at 1 year.

The EAC carried out one-way sensitivity analysis based on the EAC Scenario 1b, using EAC costs and clinical inputs . The high and low values are listed in detail in appendix F, together with their sources. Where no data was available the EAC took a +/- 20% variation. . For the costs of Endo-SPONGE and percutaneous drainage procedures, the low value used was the lower outpatients cost identified, the high value used was the day case cost used in EAC Scenario 2. Therefore the sensitivity analysis includes the possibility that initial procedures were carried out in a clinic setting, or that all procedures were carried out in theatres. In all cases the variation was at least +/- 20%, with the exception of annual stoma care costs where a low value was taken of £2896.96 (Tillin, 2005, table 5).



8.7 *The EAC's interpretation of the economic evidence*

The EAC were primarily concerned that the variability reported in the literature meant it was difficult to validate the assumptions made by the company that treatment with Endo-SPONGE avoided 35.6 operations and 16.4 permanent stomas per 100 patients. This related to the proportion of patients with anastomotic leaks who could be treated with Endo-SPONGE as well as the outcomes of non-surgical treatment of anastomotic leaks, in terms of re-operations and permanent stomas avoided

Due to the uncertainty in the clinical evidence, the EAC therefore considered a more conservative approach to the clinical parameters and assumptions in the company model should be explored. The changes made to the clinical parameter in the EAC model result in the calculation that treatment with Endo-SPONGE would avoid 9.4 re-operations and 9.4 permanent stomas per 100 patients.

The EAC also made changes to the calculation of procedure costs to avoid double counting staff time and to consider the cost implications of the

procedure settings (tables 7-10). A description of each change and its impact is included in Appendix E.

The EAC cost changes give a large reduction in the cost saving due to Endo-SPONGE at year one. If the EAC alternative clinical inputs were considered to be plausible, this would result in Endo-SPONGE being cost incurring at year one. The additional modelling by the EAC showed Endo-SPONGE becoming cost saving over a 10 year time horizon for either set of clinical inputs due to a reduction in the costs incurred for long-term stoma care. This is based on EAC Scenario 1, where Endo-SPONGE procedures are carried out in a clinic setting after the initial procedure.

If Endo-SPONGE was carried out mainly in theatre settings, it would be less likely to be cost-saving even at a 10 year time horizon

The EAC consider that due to the small number of patients per year, the possible economic impact of these uncertainties are reduced. The use of Endo-SPONGE for treating anastomotic leaks in the NHS could be considered reasonably likely to result in cost savings over a 10 year time horizon.

9 Conclusions

9.1 *Conclusions from the clinical evidence*

The conclusion of the EAC is that the evidence for Endo-SPONGE is very low quality and there is a high risk of bias due to the retrospective, non-comparative nature and small study sample sizes. The EAC notes however that as the rate of anastomotic leaks from colorectal surgery in the UK is relatively low, the quality of the studies is unlikely to be improved on.

A lack of direct comparator evidence means it is difficult to assess whether Endo-SPONGE is more effective in treating anastomotic leaks than the current standard non-surgical methods. The success rate in terms of achieving cavity closure for Endo-SPONGE treatment is high (approximately 85%) and the rate of stoma reversal following successful Endo-SPONGE treatment is approximately 77%. Clinical experts suggest that the primary benefit is likely to be in the time to stoma reversal and improvement in patient quality of life and in terms of stoma reversal this appears to bear out in the EAC review. There is very little quality of life data available however.

The populations in the Endo-SPONGE studies were largely appropriate with cancer being the primary indication for colorectal surgery. One study included patients with IPAA and it is unclear whether Endo-SPONGE would be used in such patients in the UK however it should be noted that the instructions for use do not list IPAA as a contraindication.

Risk factors for anastomotic leak are well known but the impact on treatment of leaks is unclear as the data are too limited to enable any meaningful subgroup analysis.

In conclusion, the EAC consider the evidence relating to Endo-SPONGE to be uncertain and variable, however the EAC consider this to be reflective of the clinical situation. Clinical experts report that there is no typical pathway for management of anastomotic leaks in the NHS and that decisions are made based on clinical judgement and patient condition. Endo-SPONGE appears to be a safe and effective non-surgical way to manage anastomotic leaks.

9.2 *Conclusions from the economic evidence*

The economic model shows that each Endo-SPONGE procedure and the Endo-SPONGE equipment is likely to be more costly than the non-operative alternative (modelled as percutaneous drainage), but that the cost is offset by a reduction in the number of surgical re-operations, and permanent stomas.

Reductions in re-operations can occur in the initial percentage of patients selected for non-operative treatment, and in the percentage who do not have a successful non-operative treatment and revert to re-operation. The clinical evidence supporting these inputs to the model is very uncertain, and is likely to remain so given the small number of patients eligible for this treatment.

The cost inputs also have a high degree of uncertainty, as there is not a clearly defined clinical pathway, again in part due to the small numbers of patients seen in any treatment centre annually.

Despite these uncertainties, the EAC scenarios remain cost saving over a 10 year period, where all but the initial procedure are carried out in a clinic setting

There was variation in the settings described in the literature and by clinical experts for Endo-SCOPE procedures. EAC Scenario 2 models the possibility of all Endo-SCOPE procedures taking place in theatres, which increases the cost so that it may be no longer cost saving in the 10 year horizon, dependant on the clinical inputs assumed to be most appropriate.

One implication of a move to increased Endo-SCOPE procedures may be the increased demand on endoscopy clinics. This may be difficult to accommodate for some services.

10 Summary of the combined clinical and economic sections

Endo-SPONGE appears to be a safe and effective non-surgical way to manage anastomotic leaks. The evidence for effectiveness of Endo-SPONGE compared with other non-surgical treatment of anastomotic leak is indirect but

suggests that Endo-SPONGE is at least as effective as alternative options and may reduce the number of re-operations and stoma reversals.

The economic analysis suggests that conservatively Endo-SPONGE may not be cost saving in year one but savings would be realized over a 10 year time horizon. Although there is considerable uncertainty around the economic model inputs and subsequent cost savings, the impact of this uncertainty is minimised by the small number of patients likely to be treated.

11 Implications for research

Based on a review of the evidence, the EAC do not consider that further research studies would improve the quality of the clinical evidence at this time. The clinical pathway for management of anastomotic leaks after colorectal cancer is not clearly defined and numbers of patients with this outcome in the UK is small.

12 Key Issues for Consideration

The EAC has identified a number of possible key issues for discussion:

- Anastomotic leak is a rare occurrence therefore the study sample sizes are small. While this methodologically impacts the quality of the studies, it should be highlighted that larger study sample sizes would not be achievable in this patient group.

- There is a lack of direct comparator evidence which makes it difficult to assess the clinical effectiveness of Endo-SPONGE compared with other treatment options however the evidence suggests that in isolation, Endo-SPONGE can be used successfully and safely to treat anastomotic leaks.

- The clinical pathway for the treatment of anastomotic leaks is not clearly defined. This is due to a number of factors including the small number of patients who experience an anastomotic leak, the varying definitions of anastomotic leak, lack of consistency in the grading of leak severity and clinical decisions based on patient need.

- Indirect comparison of evidence for the effectiveness of Endo-SPONGE and the effectiveness of other treatments for anastomotic leak suggest that it is possible that Endo-SPONGE may be more effective than other treatments however the extent of the difference in unclear

- Given the uncertainty in the clinical evidence, the EAC clinical parameters to the economic model present a more conservative assessment of the cost effectiveness of Endo-SPONGE. The EAC note that the company clinical parameters may also reflect the possible effectiveness of Endo-SPONGE but consider it important to consider the economic impact of alternative parameters.

- Consideration should be given to the small number of patients who are likely to be impacted by this technology. With such a small number of patients, the potential financial burden on the NHS of making this technology available is likely to be quite low.

- Clinical expert opinion suggests that the primary benefit of Endo-SPONGE is likely to be in the shorter time to stoma reversals and subsequent improvement in patient quality of life. There is no direct comparator evidence for these outcomes, however it is important to consider whether there may be a long term benefit of Endo-SPONGE which is currently not captured in the available evidence.

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14 Appendices

Appendix A: Clinical and Economic Evidence identification

Company search strategy for Outcomes for Endo-SPONGE

A literature search was performed using 5 bibliographic databases from date of inception to 5th September 2019.

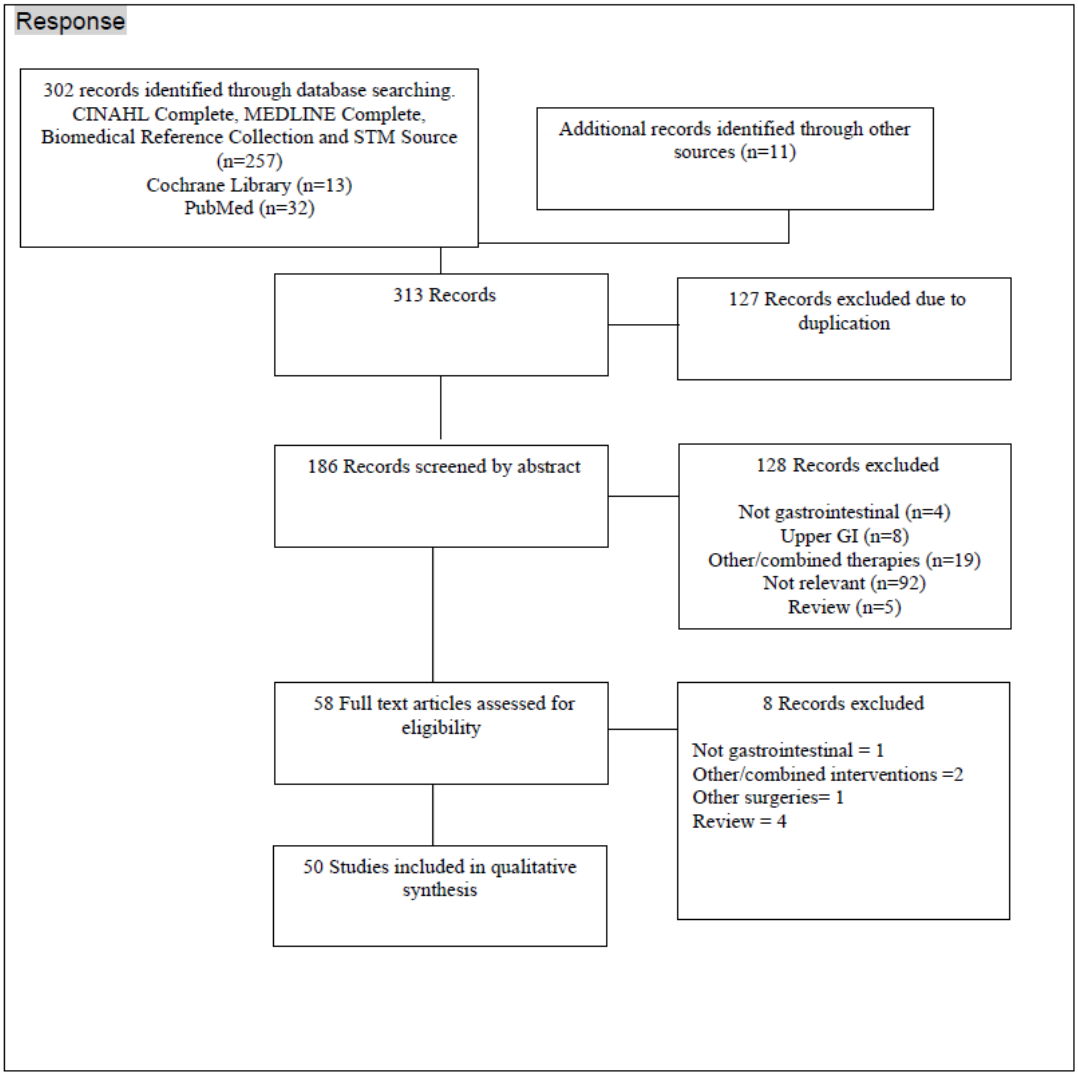
Set	Search terms	Results		
		CINAHL Complete, Medline Complete, Biomedical Reference Collection and STM	Cochrane Library	Pubmed
S1	Endo-SPONGE	162	1	25
S2	Endo-SPONGE	154	2	20
S3	Endoscopic vacuum therapy	3,829	8	337
S4	Endoscopic vacuum-assisted	1,181	10	89
S5	Transanal vacuum therapy	278	1	10
S6	ETVARD	18	0	2
S7	S1 OR S2 OR S4 OR S4 OR S5 OR S6	4,159	13	381
S8	Rectum	750,866	-	73,827
S9	Colorectal	428,841	-	165,477
S10	Rectal	40,733	-	114,163
S11	Anorectal	1,152,925	-	11,163
S12	S8 OR S9 OR S10 OR S11	1,152925	-	287,097
S13	Anastomotic leak	31,530	-	6,261
S14	S7 And S12 AND S13	605	13	32
S15	S14 NOT eosophagus	257	-	
Total = 302				

Previous company search Date: 24th December 2018 and 2nd January 2019
EMBASE and Google Scholar Endo-SPONGE or Endo-SPONGE
Limitations:

- Time period: 2012 – January 2019
- English and Spanish language

Papers not already included in initial search n= 13. These papers were included at stage for full paper analysis

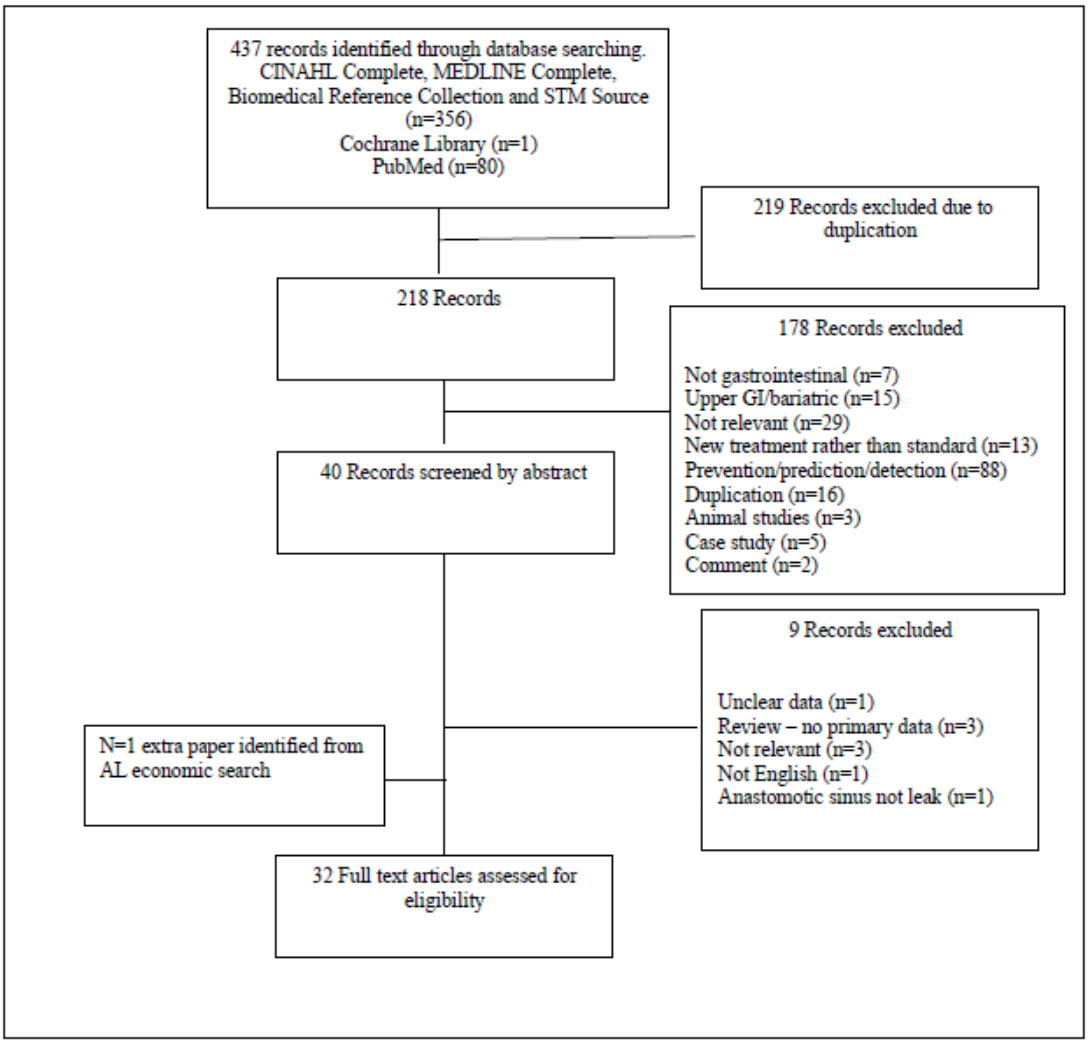
Company study selection



Company search strategy for current anastomotic leak treatments

Set	Search terms	Results		
		CINAHL Complete, Medline Complete, Biomedical Reference Collection and STM	Cochrane Library	Pubmed
S1	Anastomotic leak (TI)	1,346	1	401
S2	Anorectal (TS)	41,102	65	10,767
S3	Colorectal (TX)	760,006	348	152,107
S4	Rectal (TX)	432,350	445	112,285
S5	Rectum (TX)	299,056	233	64,992
S6	S2 OR S3 OR S4 OR S5	1,164,841	739	273,656
S7	Outcome* (TX)	8,282,063	7796	2,312,673
S8	S1 and S6 and S7	356	1	80
Total = 437				

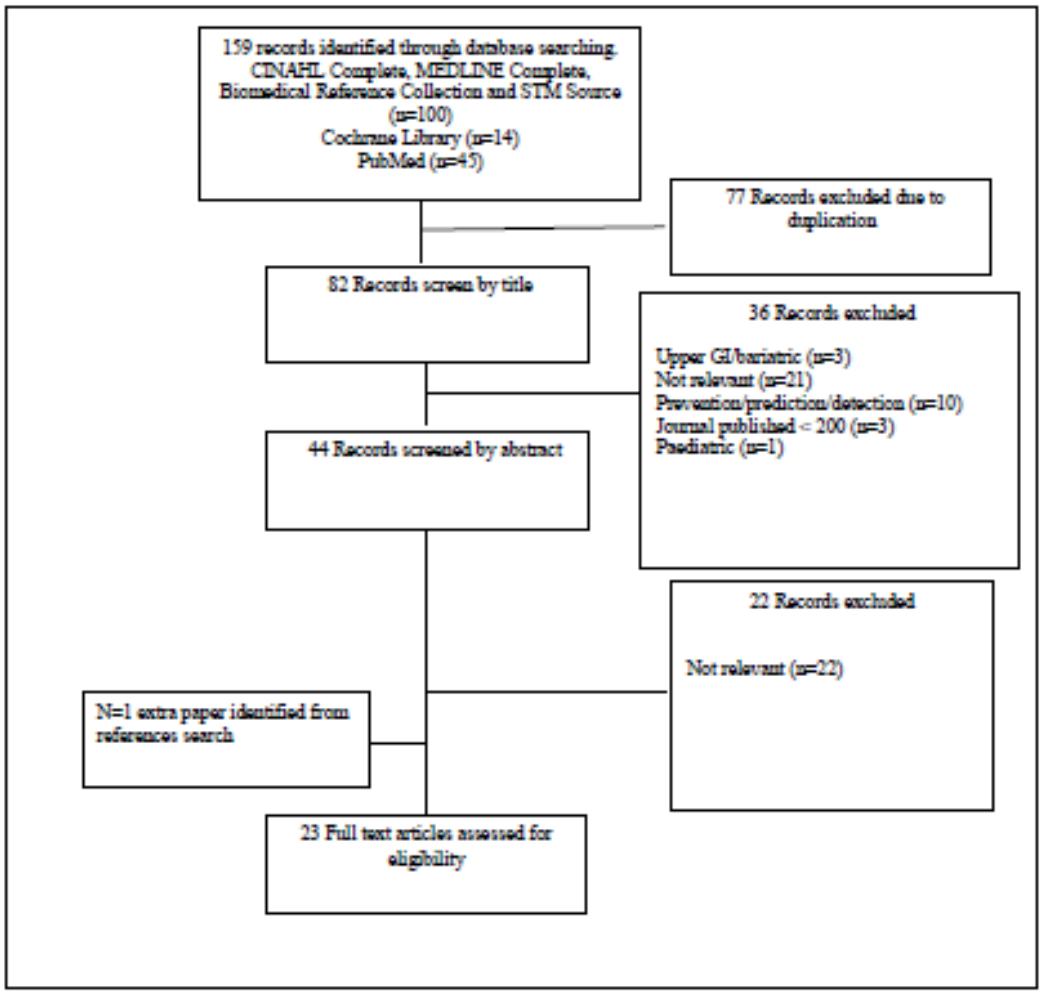
Company study selection



Company search strategy for Current anastomotic leak Economics

A literature search was performed using 5 bibliographic databases from date of inception to 23rd January 2020.

Set#	Searched	Results		
		CINAHL Complete, Medline Complete, Biomedical Reference Collection and STM	**Cochrane Library**	**Pubmed**
S1	Anastomotic leak	12,393	58	6940
S2	economic	2,060,119	2707	915006
S3	Anorectal (TX)	41,604	65	10892
S4	Colorectal (TX)	783,368	356	155533
S5	Rectal (TX)	439,403	450	113533
S6	Rectum (TX)	303,289	233	655613
S7	S3 OR S4 OR S5 OR S6	1,193,703	750	278,366
S8	S1 AND S2 AND S7	100	14	45



EAC search strategy and study selection for clinical and economic evidence

The EAC conducted a single search for both clinical and economic evidence as directed by the scope. Four bibliographic databases and 2 clinical trial registries were searched using a range of free text terms and (where appropriate) subject headings, see below for databases, search strategies and search results. The MHRA's medical device alerts and field safety notices were searched for adverse events.

Date	Database Name	Total Number of records retrieved	Total number of records from database after de-duplication
08/01/20	Cochrane Library (Wiley) CDSR CENTRAL	 0 4	
08/01/20	EMBASE (Ovid)	163	
08/01/20	Medline ALL (Ovid) – includes Medline In Process & Medline Epub Ahead of Print)	51	
09/01/20	Scopus (Elsevier)	103	
09/01/20	MHRA – search of MDA & FSN	0	
09/01/20	Clinicaltrials.gov	1	
09/01/20	ICTRP	1 (This is Borstlap 2018)	
09/01/20	Records from manufacturer website	2	
			234

Database Search strategies

Cochrane Library

ID Search Hits

#1 (Endo-sponge or Endo-SPONGE):ti,ab,kw (Word variations have been searched) 2

#2 ("vacuum-assisted therapy"):ti,ab,kw (Word variations have been searched) 0

#3 (vacuum-assisted NEAR/3 closure):ti,ab,kw (Word variations have been searched) 377

#4 MeSH descriptor: [Negative-Pressure Wound Therapy] this term only 173

#5 MeSH descriptor: [Surgical Sponges] this term only 89

#6 #2 or #3 or #4 or #5 569

#7 ("Anastomotic leak*" or anastomos*):ti,ab,kw (Word variations have been searched) 4713

#8 MeSH descriptor: [Anastomosis, Surgical] this term only 734

#9 MeSH descriptor: [Anastomotic Leak] this term only 130

#10 #7 or #8 or #9 4713

#11 ((colorectal or rectal) NEAR/3 (surgery or excis* or resect*)):ti,ab,kw (Word variations have been searched) 5800

#12 MeSH descriptor: [Colectomy] this term only 593

#13 MeSH descriptor: [Colonic Neoplasms] this term only and with qualifier(s): [surgery - SU] 501

#14 MeSH descriptor: [Rectal Neoplasms] this term only and with qualifier(s): [surgery - SU] 766

#15 #11 or #12 or #13 or #14 6512

#16 #6 and #10 and #15 3

#17 #1 or #16 4

Results = Central Register of Controlled Trials: 4; CDSR: 0

EMBASE <1947-Present>

1 (Endo-sponge or Endo-SPONGE).tw. (105)

2 ("vacuum-assisted therapy" or (vacuum-assisted adj3 closure)).tw. (1833)

3 vacuum assisted closure/ (6531)

4 surgical sponge/ (1301)

5 or/2-4 (8173)

6 ("Anastomotic leak*" or anastomos*).tw. (118872)

7 anastomosis/ (51210)

8 anastomosis leakage/ (18405)

9 or/6-8 (138373)

10 ((colorectal or rectal) adj3 (surgery or excis* or resect*)).tw. (38558)

11 colon surgery/ (4751)

12 colon resection/ (32520)

13 rectum surgery/ (5967)

14 rectum tumor/su [Surgery] (6714)

15 colon cancer/su [Surgery] (5581)

16 or/10-15 (82301)

17 5 and 9 and 16 (79)

18 1 or 17 (163)

Ovid MEDLINE(R) ALL <1946 to January 07, 2020>

1 (Endo-sponge or Endo-SPONGE).tw. (31)

2 ("vacuum-assisted therapy" or (vacuum-assisted adj3 closure)).tw. (1221)

3 Negative-Pressure Wound Therapy/ (2789)

4 Surgical Sponges/ (1524)

5 or/2-4 (4814)

6 ("Anastomotic leak*" or anastomos*).tw. (69413)

7 Anastomosis, Surgical/ (30506)

8 Anastomotic Leak/ (3204)

9 or/6-8 (81624)

10 ((colorectal or rectal) adj3 (surgery or excis* or resect*)).tw. (20874)

11 Colectomy/ (17297)

12 Colonic Neoplasms/su [Surgery] (11239)

13 Rectal Neoplasms/su [Surgery] (18367)

14 10 or 11 or 12 or 13 (52159)

15 5 and 9 and 14 (30)

16 1 or 15 (51)

Scopus

TITLE-ABS-KEY (endo-sponge OR Endo-SPONGE)) OR ((TITLE-ABS-KEY ("vacuum-assisted therapy" OR (vacuum-assisted W/3 closure)) AND TITLE-ABS-KEY ("Anastomotic leak*" OR anastomos*) AND TITLE-ABS-KEY ((colorectal OR rectal) W/3 (surgery OR excis* OR resect*))))

Results 103

Clinicaltrials.gov

Endo-SPONGE or endo-sponge

Results = 1 relevant

ICTRP

Endo-SPONGE or endo-sponge

Results = 1

MHRA

Endo-SPONGE or endo-sponge

Results = 0

EAC study selection

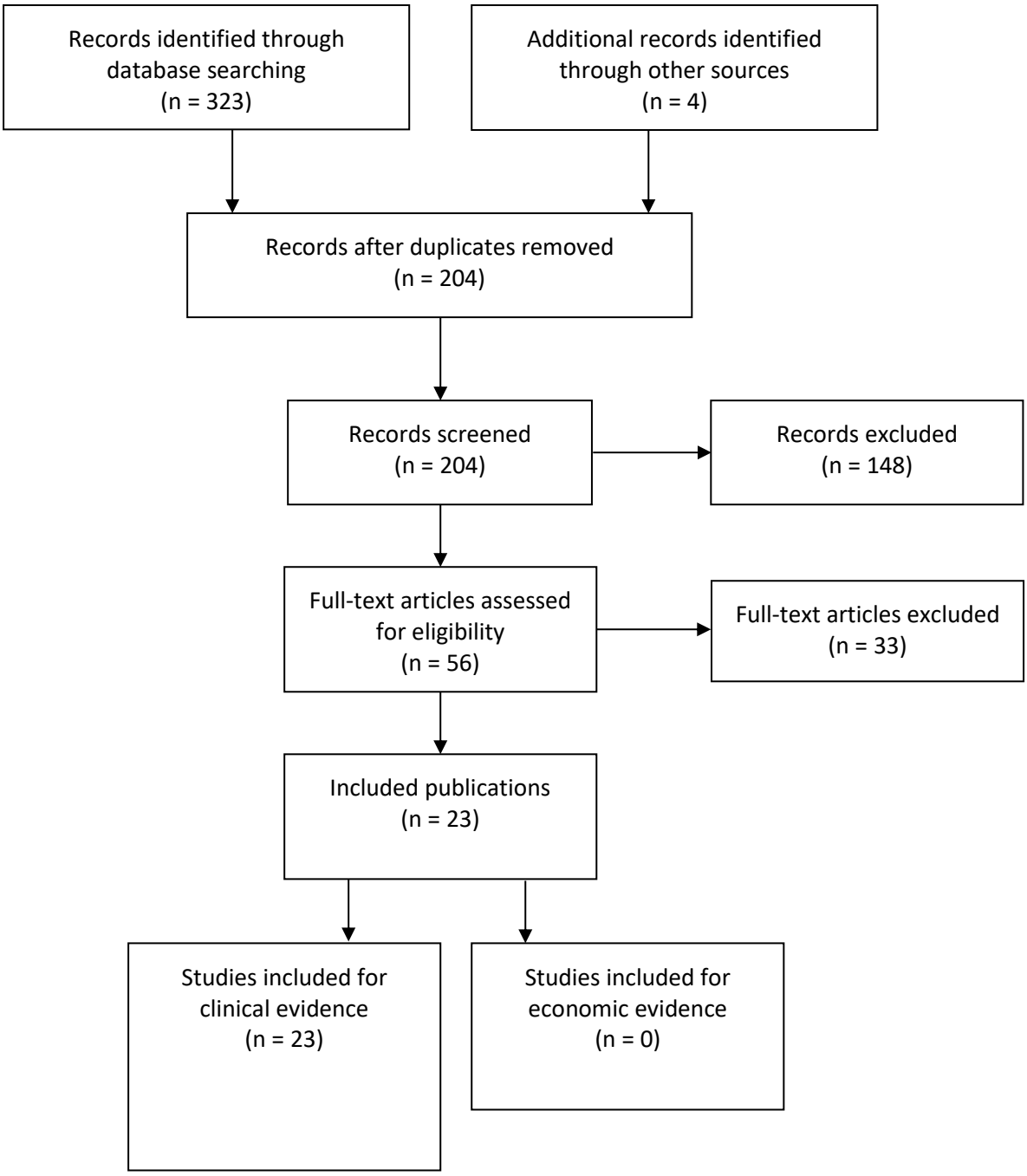


Table: EAC included and excluded studies with reasons (comparison between company and EAC included studies)

Study	Included in Company Submission	Included by EAC	EAC Comment
Arezzo (2015)	✓	✓	
Borschetti et al. 2018	✓	✓	This study was not identified by EAC searches as it does not appear to be indexed in the databases.
Borstlap (2018)	X	X	Reason for company exclusion suggests Endo-SPONGE effect cannot be assured as study includes other therapies. EAC considers that as the clinical pathway is variable and may include combination therapies/treatments this may be relevant. Review of the study by the EAC indicates a cross-over of one study centre with two other studies (Gardenbroek 2015 and Huisman 2019) and have therefore excluded it from the review in favour of the more recent Huisman 2019 study.
Buzzi (2012)	X	X	Abstract Only Not listed in company submission EAC excluded due to overlap with full publication (Mussetto, 2017)
Campanelli (2017)	X	X	Abstract Only Not listed in company submission EAC excluded due to overlap with full publication (Milito, 2017)
Clifford (2019)	✓	X	Systematic review has been included in the company submission (data extraction tables) however the results are not discussed. The EAC have excluded this as it was assessed as being a very low quality review and included non-Endo-SPONGE studies.
Di Mitri (2010)	X	✓	Abstract Only. The EAC has included this abstract as there is no evidence that it overlaps with any other publication at this time.
Ewart	X	X	Abstract Only The EAC cannot conclude the Endo-SPONGE was used
Gardenbroek (2013)	X	X	Abstract Only Excluded due to possible overlap with full publication (Gardenbroek, 2015).
Gardenbroek (2015)	X	X	Abstract Only

			Excluded from company submission because Endo-SPONGE effect cannot be assured as study includes other therapies. The EAC note that one systematic review which the company included in their submission (Shalaby et al. 2019) included this study. The EAC considers that as the clinical pathway is variable and may include combination therapies/treatments, however also note that there is possible overlap with Wasmann (2019).The EAC have excluded this abstract in favour of Wasmann (2019) which is a full publication with more participants.
Huisman (2019)	✓	✓	
Jiménez-Rodríguez (2018)	✓	✓	
Katz (2018)	✓	✓	
Keskin (2015)	✓	✓	
Kuehn (2015)	X	X	Abstract Only Not listed in company submission EAC excluded due to overlap with full publication (Kuehn, 2016)
Kuehn (2016)	✓	✓	
Lisi (2017)	X	X	Abstract Only Not listed in company submission EAC excluded due to overlap with full publication (Milito, 2017)
Manta (2016)	✓	✓	The EAC note that there is a possibility of patient over-lap between this and Strangio et al but cannot determine which patients/outcomes may be affected.
Martel (2013)	X	✓	Abstract Only The EAC has included this abstract as there is no evidence that it overlaps with any other publication at this time.
McAuley (2013)	X	✓	Abstract Only The EAC has included this abstract as there is no evidence that it overlaps with any other publication at this time.
Mencio (2018)	X	X	Not Endo-SPONGE by BBraun. Intervention is called 'Endo-SPONGE' however the EAC conclude that it is not Endo-SPONGE by BBraun based on the information in the publication.
Milito (2012)	X	X	Abstract Only Not listed in company submission EAC excluded due to overlap with full publication (Milito, 2017)

Milito (2015)	X	X	Abstract Only Not listed in company submission EAC excluded due to overlap with full publication (Milito, 2017)
Milito (2017)	✓	✓	
Mussetto (2017)	✓	✓	
Nerup (2013)	✓	✓	
Popivanov (2019)	✓	X	The EAC have excluded this review as appraisal suggests it is critically low quality. The EAC have instead included the individual studies for review.
Repici (2013)	X	X	Abstract Only Not listed in company submission EAC excluded due to overlap with full publication (Strangio, 2015)
Riss, Stift, Kienbacher (2009)	✓	✓	The EAC note that there is possible overlap between the patients in this study and Riss et al (2010), however there is no way to determine which patients/outcomes may be affected.
Riss, Stift, Meier (2010)	✓	✓	
Rottoli (2018)	✓	✓	
Schiffmann (2019)	X	✓	
Shalaby (2019)	✓	X	The EAC have excluded this review as appraisal suggests it is very low quality. The EAC have instead included the individual studies for review.
Sileri (2016)	X	X	Abstract only Does not mention Endo-SPONGE
Srinivasamurthy (2013)	✓	✓	
Strangio (2015)	✓	✓	
van Koperen (2009)	✓	✓	
Wasmann (2019)	X	✓	
Weidenhagen (2008)	✓	✓	There are inconsistencies in the company submission regarding the referencing of this study. There appear to be three publications referenced in the company submission. The EAC note that the three publications listed in the company submission are: • Weidenhagen, R., K. U. Gruetzner, T. Wiecken, F. Spelsberg, and K. W. Jauch. 2008a. 'Endoluminal vacuum therapy for the treatment of anastomotic leakage after anterior rectal

			resection', Rozhledy V Chirurgii: Mesicnik Ceskoslovenske Chirurgicke Spolecnosti, 87: 397-402. • ———. 2008b. 'Endoscopic vacuum-assisted closure of anastomotic leakage following anterior resection of the rectum: a new method', Surg Endosc, 22: 1818-25. • Weidenhagen, Rolf, Klaus Uwe Gruetzner, Timm Wiecken, Fritz Spelsberg, and Karl-Walter Jauch. 2008c. 'Endoscopic vacuum-assisted closure of anastomotic leakage following anterior resection of the rectum: a new method', Surg Endosc, 22: 1818-25. The EAC note that in table 1 of the company submission, Weidenhagen et al 2008a is listed as the relevant study however in the summary tables which follow in table 4 and again in section 5, the Weidenhagen study included is 2008c. The EAC not that in the reference list, Weidenhagen 2008b and 2008c are the same reference. The EAC cannot determine with any certainty which publications have been used throughout the company submission and after review of the individual studies concluded that the only relevant study is • Weidenhagen, Rolf, Klaus Uwe Gruetzner, Timm Wiecken, Fritz Spelsberg, and Karl-Walter Jauch. 2008c. 'Endoscopic vacuum-assisted closure of anastomotic leakage following anterior resection of the rectum: a new method', Surg Endosc, 22: 1818-25. This is because • Weidenhagen, R., K. U. Gruetzner, T. Wiecken, F. Spelsberg, and K. W. Jauch. 2008a. 'Endoluminal vacuum therapy for the treatment of anastomotic leakage after anterior rectal resection', Rozhledy V Chirurgii: Mesicnik Ceskoslovenske Chirurgicke Spolecnosti, 87: 397-402. is essentially a narrative review and does not report any detail on the patients in the study.

Clifford et al., 2019 is a Critcially Low quality review

1. Did the research questions and inclusion criteria for the review include the components of PICO?	No
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No
3. Did the review authors explain their selection of the study designs for inclusion in the review?	No
4. Did the review authors use a comprehensive literature search strategy?	Partial Yes
5. Did the review authors perform study selection in duplicate?	No
6. Did the review authors perform data extraction in duplicate?	Yes
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No
8. Did the review authors describe the included studies in adequate detail?	No
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	
RCT	0
NRSI	No
10. Did the review authors report on the sources of funding for the studies included in the review?	No
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	
RCT	0

NRSI	0
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	0
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	No
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	No
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	0
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes

Popivanov et al. 2019 is a Critically Low quality review

1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No
3. Did the review authors explain their selection of the study designs for inclusion in the review?	No
4. Did the review authors use a comprehensive literature search strategy?	No
5. Did the review authors perform study selection in duplicate?	Yes
6. Did the review authors perform data extraction in duplicate?	No
7. Did the review authors provide a list of excluded studies and justify the exclusions?	Yes
8. Did the review authors describe the included studies in adequate detail?	No
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	
RCT	0
NRSI	No
10. Did the review authors report on the sources of funding for the studies included in the review?	No

11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	
RCT	0
NRSI	0
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	0
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	No
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	No
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	0
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes

Shalaby et al., 2019 is a Low quality review

1. Did the research questions and inclusion criteria for the review include the components of PICO?	No
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Partial Yes
3. Did the review authors explain their selection of the study designs for inclusion in the review?	No
4. Did the review authors use a comprehensive literature search strategy?	Partial Yes
5. Did the review authors perform study selection in duplicate?	Yes
6. Did the review authors perform data extraction in duplicate?	Yes
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No
8. Did the review authors describe the included studies in adequate detail	Partial Yes
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	
RCT	0
NRSI	Partial Yes
10. Did the review authors report on the sources of funding for the studies included in the review?	No
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	

RCT	0
NRSI	0
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	0
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	No
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	No
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	0
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes

Appendix B –Data Extraction

Study name,location, duration	Design and intervention(s)	Participants and setting	Outcomes	Results	EAC comments
Full text					

Arezzo (2015) Italy (single centre) November 2008 to June 2013	Retrospective Case series. Endo-SPONGE. Device replaced two or three times a week until complete healing of dehiscence was achieved. All chronic cases were treated as outpatient; acute were initiated on inpatient basis and discharged if the general conditions were favourable to proceed as outpatient. Minimum follow-up – 1 year Authors declare no conflicts of interest. Status of study: published. Endo-SPONGE ● No comparator ●	N=14 (5 male, 9 female). Median age 68 years old (range 55-85). 12 leaks after rectum anterior resection, 1 leak after transanal endoscopic microsurgery and 1 recto-vaginal fistula after a stapled transanal resection of the rectum. Median distance from the anal verge was 5 cm (range 3-9 cm). Radiotherapy used in 7/14 (50%). Derivative stoma in 8/14 (57.1%). Chronic leak in 4/14 (28.6%) Median cavity length 4cm (2-9cm) Single centre Inclusion criteria: all patients with acute or chronic leak in the presence of extraluminal abscess (November 2008 – June 2013) Exclusion criteria: presence of generalized peritonitis or haemodynamically unstable patient was a contraindication to endoscopic treatment ●	Success rate (direct endo-scopic examination with the aid in all cases of direct water soluble contrast infection during endoscopy, showed a complete restoration of the wall epithelium.) Reasons for treatment failure Time to complete healing Number of sessions required (treatment sessions) ●	Overall Success Rate 79% (11/14) • 89% (9/10) in acute leaks (<60 days) and 50% (2/4) in chronic leaks (>60 days) (p=0.176). • Success in 100% (8/8) of patients with stoma and 50% (3/6) in patients without it (p=0.055) Success in 71% (5/7) of patients after radiotherapy and 86% (6/7) among untreated (p=1) Time to treatment completion Median time to complete healing 40.5 days (8-114) Number of sessions Median number of treatment sessions 12.5 (range 4-40) Length of Stay For patients with acute leaks, initial treatment was on an inpatient basis with patients discharged within 1 week to continue treatment as outpatients if appropriate Chronic leaks all treated on an outpatient basis	Small case series, retrospective design, single centre. No comparator. Data in text and table don't match (sex distribution). One patient presented with recto-vaginal fistula.

Study name,location, duration	Design and intervention(s)	Participants and setting	Outcomes	Results	EAC comments
Boschetti (2018) France (2 centres) January 2013 to December 2016	Retrospective case series January 2013 to December 2016 Endo-SPONGE Endo-SPONGE treatment was started in the month following surgery in 12 cases, and the mean delay was 35±56 weeks (8-260 weeks) in the remaining cases. These were cases referred from other centres due to failure of surgical or radiological treatments. Patients followed up endoscopically at 1, 3 and 6 months after treatment Authors report no conflict of interest Status of study: published. Endo-SPONGE ● No comparator ●	N=29 patients (22 male, 7 female) Mean age 68±10 years (range 51 – 88) 23 with rectal cancer and 19 with neo-adjuvant chemoradiotherapy 3 sigmoiditis (1 left colonic cancer 2 right colonic cancer with peritoneal carcinosis treated by hyperthermic intraperitoneal chemotherapy and left colectomy with colorectal anastomosis) Fistula was detected after sepsis in 25/29 (86.2%) patients, rectal bleeding in 6.9% (n=2), and diarrhoea in 3.4% (n=1). Mean fistula length was 7cm±4.6cm (2-20cm) Mean distance from anal verge was 6.2cm±4.6cm (2-20cm) At inclusion stage, 21 patients were referred for Endo-SPONGE treatment with a stoma systematically performed at the time of anastomosis (n=12) or secondly to treat sepsis (n=9). N=12 patients were taking antibiotics when Endo-SPONGE was performed Nutritional support was used in 3 patients	Unclear,the outcomes are not defined in the methods of the study but the results report: Time to closure Number of sessions Success rate Reversal of protective stoma ●	Overall success rate 93% (27/29) success (closure of cavity to <1cm) 24/29 successfully closed at 6 months Stoma reversal/continuity restored At 6 months, 85.7% (n=18) of patients presenting with a stoma had closure of stoma Time to completion Mean time to treatment to closure 10±6.5 (range 2-28) weeks Number of sessions Mean number of treatment session was 18.6 ±13 (range 4-57) Complications 1 patient with colon perforation following attempt to increase fistula size to facilitate endo-SPONGE treatment Length of stay Not applicable All patients treated on an outpatient basis	Retrospective Small sample size No comparator

Huisman (2019) Netherlands (2 centres) January 2012 to August 2017	Retrospective Case series. Endo-SPONGE with surgical closure (surgical closure at the preference of the surgeon).. Depending on size of cavity 1-3 were placed in deepest point of presacral cavity with pressure of 150 mmHg, sponges were change twice/week. At 1st placement surgeon and gastroenterologist placed sponges, subsequent placements were made by gastroenterologist alone. Depending on surgeon preference, transanal closure of the defect was performed after a short period of Endo-SPONGE therapy (vacuum-assisted early transanal closure) to achieve shorter Endo-SPONGE therapy duration. Start of follow-up was primary resection and end of follow-up was date of interest; stoma reversal date, last Endo-SPONGE exchange date, date of death or end of follow-up. End of follow-up for patients without stoma reversal or not censored was last hospital visit. Median follow-up was 10 months (3-84) Authors declare no conflict of interest. Status of study: published.	N=20 (14 male, 6 female); median age 64 years (SD 10). Indication: 18 rectal cancer; 2 inflammatory bowel disease. 2 colorectal cancer centres. Jan 2012 to Aug 2017. Inclusion/exclusion criteria: all eligible patients with symptomatic AL after rectal surgery treated with Endo-SPONGE therapy were included. Patients with postoperative signs of AL and AL confirmed by computed tomography (CT) scan were considered eligible. Patients with colonic cancer, patients who underwent Hartmann's procedure as primary surgical procedure and patients who underwent transanal endoscopic microsurgery (TEM) were excluded. ●	Primary outcome: restored gastrointestinal continuity at end of follow-up. ● Secondary outcomes: success rate; presence of a chronic sinus and the functional bowel outcome after AL (LARS score). ●	Success rate 85% (17/20) (reduction of cavity with complete granulation) N=3 patients had planned surgery after a median 2 Endo-SPONGE treatments Mortality 0 related to Endo-SPONGE (1 unrelated) Stoma reversal/bowel continuity 70% (14/20) Complications Chronic sinus developed in 3 (15%) patients who received a definitive stoma. Quality of Life Quality of life: 3 patients (23%) had minor LARS, 10 patients (77%) had major LARS.	The study intervention was Endo-Sponge alone of Endo-SPONGE followed by a surgical closure of defect for some patients. Small case series (high risk of bias). No comparator.

Study name,location, duration	Design and intervention(s)	Participants and setting	Outcomes	Results	EAC comments
	Endo-SPONGE + Surgical closure ● no comparator ●				

Jiménez Rodríguez (2018) Spain (single centre Study period not reported	Case series (unclear, possible prospective). Endo-SPONGE. Depending on size of cavity 2 or more were used. Initially pressure of 375 mmHg was used and modified to 150 mm Hg at the first sponge replacement, sponges were changed every 3 – 5 days. In all patients, the first treatment was performed in-hospital, but the successive replacements were carried out on an outpatient basis for 11 patients. For 10 patients fibrin glue was used in addition after VAC therapy was over and once the diameter of the cavity was too small to allow entry of the sponge. Follow-up began at the time treatment stopped following cavity closure. Mean follow-up period was 12.36±7.9 months Funding provided by Instituto de Salud Carlos III, Madrid, Spain. Status of study: published. Endo-SPONGE ● No comparator ●	N=22 (18 male, 4 female); median age 64.8 years (SD 9.90). Indication: colorectal cancer, 13 underwent anterior resection and colorectal anastomosis, and 9 underwent Hartmann's procedure Tertiary hospital. Dates of procedure/data collection not provided. Inclusion/exclusion criteria: patients scheduled to undergo VAC therapy for dehiscence of lower colorectal anastomosis or opening of the rectal stump after anterior resection for rectal cancer were included. Patients with severe signs of systemic inflammatory response that needed immediate intensive treatment were excluded as were those with cavities that had a size less than 2 × 2 cm. ●	The following were recorded: complications during the procedure and until wound healing was complete, recurrence rate in cases of cancer, mortality rate, and length of hospital stay, number of devices used in each patient, the number of days of treatment, the size of the cavity at onset of therapy, the number of days elapsing from surgery to the diagnosis of anastomotic dehiscence or rectal stump leakage, and those from diagnosis to the end of therapy. ●	Overall success rate 91% (20/22) (cavity closure) Full resolution was achieved without further surgery for a total of 19 patients, who were followed- up for a minimum period of 1 year. Mortality 0 related to Endo-SPONGE (3 unrelated) Stoma reversal/continuity restored 5/13 (38.46%) Time to completion Mean time to achieve healing: 22.3 ± 14.7 days; 24.0 ± 15.5 days for the anterior resection group and 19.8 ± 14.09 days for the Hartmann group. Number of sessions Mean number of endoscopic sessions per patient: 3.1 ± 1.9 in the anterior resection group and 3.2 ± 1.8 in the Hartmann group. Complications None during procedure In 2 patients (both from the anterior resection with ileostomy group), closure	Small case series (high risk of bias). No comparator. Dates of procedure/data collection not provided. For 10 patients fibrin glue was used after VAC therapy (once diameter of the cavity was too small to insert a sponge) – this is not related to the success of the endo-SPONGE treatment.

Study name,location, duration	Design and intervention(s)	Participants and setting	Outcomes	Results	EAC comments
				was not achieved, necessitating surgical intervention	
Katz (2018) Israel (single centre) May 2014 to December 2016	Retrospective Case series. Endo-SPONGE. In 5 cases insertion was manual (under sedation) and in 1 case via TAMIS approach (under general anaesthesia) after the failure of endoscopic insertion. All procedures were performed in the operating room. A diverting stoma was constructed in 2/3 patients who had no previous diversion. One patient was treated with endo-sponge and antibiotics with no need for diversion. No patient underwent irradiation prior to treatment. Sepsis control was achieved following the initial treatment (antibiotics, Endo-SPONGE, and diversion). Median duration of follow-up was 28 months (18-32) Authors declare no conflict of interest. Status of study: published. Endo-SPONGE ● No comparator ●	N= 6 (5 male, 1 female); median age 63 years (SD 20.3). Indications as follows: low rectal cancer; rectal villous adenoma; Hirschsprung; familial adenomatous polyposis; ovarian cancer with rectal involvement. Median dehiscence 180 (degrees) range 50-270 degrees Median time to leak diagnosis 7 days (range 4-14 days). Median time to first sponge placement 13 days (range 9-33)Hospital. May 2014 to Dec 2016. Inclusion/exclusion criteria: not reported. ●	A priori outcome measures not reported in the methods. Results include reporting of • success rate • restoration of bowel continuity • number of sponge exchanges ●	Overall success 100% (6/6) (fully recovered) 1 patient treated with endo-SPONGE and antibiotics Stoma reversal 4/5 Number of sessions Mean number of exchanges: 3.6 (range 3–5 exchanges)	Very small case series (high risk of bias). No comparator. Inclusion/exclusion criteria not reported. Discrepancy in reporting of stoma numbers between table and text of the study (table suggests 3/5 had a stoma already and 1/5 had a stoma created following leak diagnosis).

Study name,location, duration	Design and intervention(s)	Participants and setting	Outcomes	Results	EAC comments
Keskin (2015) Turkey (single centre) May 2009 to May 2014	RetrospectiveCase series Endo-SPONGE. Applied in n endoscopy unit under sedation by a surgeon. The sponge was changed every 3 – 4 days. Average number of sponge applications was 2.2 (range, 1 to 5). 12 patients treated as in-patients and 3 as out-patients. Follow-up duration period not reported. Authors declare no conflict of interest. Status of study: published. Endo-SPONGE ● No comparator ●	N=15 (8 female, 7 male), average age 55 years (25-72). Indications: rectal tumour (n=12); familial polyposis coli (n=2); diverticular disease (n=1).Eight leaks were identified early and 7 leaks identified late Hospital (in an endoscopy unit) May 2009 and May 2014. Inclusion/exclusion criteria: patients deemed suitable for Endo-SPONGE treatment who developed AL after protectomy were included. Patients with cavities opening to the abdomen due to low rectal anastomotic leakages were excluded. ●	Cavity closure Results were also reported for lumen integrity, stoma closure rate, impact of early and late diagnosis on treatment success and any recurrent abscesses although these were not listed as outcomes in the methods ●	Overall success rate 80% (12/15) (sufficient granulation) Mortality 0 related to Endo-SPONGE (3 unrelated) Stoma reversal/bowel continuity 10/14 Number of sessions Average number of sponge applications was 2.2 (range, 1 to 5)	Small case series (high risk of bias). No comparator.

Study name,location, duration	Design and intervention(s)	Participants and setting	Outcomes	Results	EAC comments
Kuehn (2016) Germany (single centre) 2007-2015	Retrospective Case series. Endo-SPONGE. Inpatient or outpatient therapy. Placement was carried out in the surgical endoscopy unit, in the operating room or on the intensive care unit. Sponges were changed after 3 days. EVT usually performed without the need for sedation or anaesthesia Mean follow-up was 36 months (2-89) Conflicts of interest not reported. Status of study: published. Endo-SPONGE ● No comparator ●	N=20. Median age of 70 years (range 29-91) of entire cohort. Indication: an extraperitoneal anastomotic leakage after rectal or rectosigmoid resection 20/20 (rectal or rectosigmoid cancer 16/20, diverticulitis 2/20, recurrent perforating diverticulitis 1/20, iatrogenic perforation 1/20). Radio- or radio-chemotherapy used in 75% of cancer patients. Single centre Inclusion criteria: patients with defects of lower gastrointestinal tract showing the signs of anastomotic leakage or rectal lesion. Considered for patients with signs of a localized peritonitis of the lower abdomen (September 2007 – February 2015) Exclusion criteria: operative revision was indicated for patients with signs of a generalized peritonitis ●	Success Closure of enterostomy and reasons for failure Adverse events Time to leakage detection Therapy duration Number of sponges used ●	Overall success 90% (18/20) (not reported) Stoma reversal/bowel continuity 15/19 Time to completion 23 days (range 2-109) Number of sessions Number of sponge insertions 7 (1 - 37) for anastomotic leak population	Small sample size, retrospective design, single centre. No comparator. No information regarding conflict of interests.

Study name,location, duration	Design and intervention(s)	Participants and setting	Outcomes	Results	EAC comments
Manta 2016 Italy (2 centres) April 2009 to September 2014	Retropsective Case series. Endo-SPONGE. Periodically changed until fistula closure was achieved. The initial positioning in hospital, changes performed in outpatient setting. Single or multiple devices were used. Follow-up not reported Authors declare no conflict of interest. Status of study: published. Endo-SPONGE ● No direct comparator but some patients were treated using over the scope clips (OTSC) or OTSC plus stents. ●	N=7. Fistula type: 6 delayed, 1 early with diameter ranged 15 – 50m. 4 underwent anterior rectal resection, 2 left colectomy, 1 total colectomy. 2 Endoscopic Units, 7/7 in out-patients setting. N=18 treated with OTSC and N=4 treated with OTSCO+Stent Inclusion criteria: patients with a post-surgical leak referred by the surgeon for an initial endoscopic attempt in order to avoid re-intervention (April 2009 – September 2014). ●	Fistula closure Length of stay was an outcome for the whole study cohort but not applicable to Endo-SPONGE as these were all outpatients ●	Overall success 100% (7/7) (complete leakage closure)	The study was not designed to investigate what method of closure was most effective therefore comparisons have not been made between the different treatment types. Baseline characteristics were not presented for Endo-SPONGE patients only. Small case series (high risk of bias), retrospective design. Possible overlap with Strangio (2015) as one study centre is the same.

Study name,location, duration	Design and intervention(s)	Participants and setting	Outcomes	Results	EAC comments
Milito (2017) Italy (single centre) January 2007 to December 2014	Retrospective Case series. Endo-SPONGE. Mean anastomosis level was 5 cm (3-7). Patients received an intravenous antibiotic therapy with piperacillin+tazobactam (4.5g, 3 times/daily). Median size of the cavity was 81x46 mm Median time to leak diagnosis 14 days (range 7-21) Follow-up not reported Authors declare no conflict of interest. Status of study: published. Endo-SPONGE ● No comparator ●	n=14 (10 male, 4 female). Mean age 72 years (42-81). Indication: malignancy (rectal cancer) 14/14. Preoperative radiotherapy 14/14. Stoma created during primary surgery 14/14. Single centre Inclusion criteria: patients with anastomotic leakage following low anterior resection; dimension of the cavity >1x0.5 cm 9impossibility to insert the sponge; age of patients <85 years; rectal anastomosis <7cm from anal verge (difficult placement); loop ileostomy during the previous surgery (January 2007 – December 2014) Exclusion criteria: diffuse peritonitis; nonednoscopically accessible septic focus; malignant tumour wound; untreated osteomyelitis ●	Time to diagnosis of anastomotic leakage Time of the outpatient therapy Sponge exchanges for each patient Healing time Complications and side effects ●	Time to completion Median healing time was 37 days (19-55) Median time of the outpatient therapy was 35 days (16-51) Number of sessions Between 3-14 sponge exchanges for each patient Complications No intraoperative complications. No specific side effects during or after the therapy. N=5 had mild anal pain successfully treated medically.	Data in the table does not match information in the text (mean age) Small number of patients, observational study, single centre. Retrospective design.

Study name,location, duration	Design and intervention(s)	Participants and setting	Outcomes	Results	EAC comments
Mussetto (2017) Italy (single centre) March 2010 to February 2015	Retrospective Case series. Endo-SPONGE. The therapy was performed under conscious sedation (meperidine (0.5-1mg/kg IV) and midazolam (2.5-5 mg IV)). The sponges were changed every 48-72 h. Closure was defined as a decreased cavity covered with granulation tissue that did not allow the insertion of a new sponge. Mean distance of anastomosis from anal verge was 4.5 cm (range 2-8). Mean size of leakage was 7.5 cm (range 4-12). Mean follow-up was 29 months (6-64) Authors declare no conflicts of interest. Status of study: published. Endo-SPONGE ● No comparator ●	N=11 (6 male, 5 female). Mean age 71 years old (range 55 – 82). Indication: 11/11 rectal cancer. Neoadjuvant radio/chemotherapy in 5/11. Single centre Inclusion criteria: Patients with anastomotic leakage (March 2010 – February 2015) ●	Number of treatments Number of days from treatment to closure Closure of anastomotic leakage Treatment failure Relapse of leakage Complications Follow-up time Mortality ●	Overall success Closure of leakage was achieved in 10/11 (90.9%) (decreased cavity covered with granulation tissue preventing insertion of further sponges) Mortality 0 related to Endo-SPONGE (2 unrelated) Number of sessions Mean number of treatments was 16 (range 9-23) Complications During follow-up complications were observed in 2/11 (18%; stenosis in both)	Small number of patients, retrospective design, single centre. No comparator. Lack of exclusion criteria.

Study name,location, duration	Design and intervention(s)	Participants and setting	Outcomes	Results	EAC comments
Nerup (2013) Denmark (2 centres) February 2008 to 2012	Retrospective Case series. Endo-SPONGE. The sponge was changes every second or third day. Treatment was ceased when the cavity was about 3 cm wide and covered in granulation tissue. Median tumour distance from anus was 9 cm (6-12). Inpatient stay, some continued treatment as outpatient. Follow-up not reported Authors declare no conflicts of interest. Status of study: published. Endo-SPONGE ● No comparator ●	N=13 (11 males, 2 females). Median age was 64 years (range 36-71). ASA classification: I 4/13 (31%), II 9/13 (69%). Indication: 13/13 (100%) rectal cancer. Primary ileostomy 13/13 (100%). Neoadjuvant radiotherapy 6/13 (46%). Two centres Inclusion criteria: patients with rectal cancer following low anterior resection of the rectum who developed an anastomotic leak and were treated with endoscopic vacuum therapy; patients who could be managed without re-laparotomy (1st of Feb 2008 – 1st of Feb 2012) Exclusion criteria: late onset endoscopic vacuum treatment more than one month after leakage diagnosis and patients who had not completed treatment at 1st of Feb 2012; patients who required re-laparotomy ●	Treatment success Hospital stay Number of treatments Length of treatment Mortality Complications Stoma closure rate ●	Overall success Healing of the perianastomotic abscess cavity was successful in 13/13 (100%) (successful healing) Mortality 0 related to Endo-SPONGE Stoma reversal/continuity restored Stoma closure rate was 12/13 (92%) Time to completion Median length of stay was 25 days (7-39) and treatment continued for a median 18 days (340 days) Number of sessions Median number of treatments per patient was 8 (1-18) Complications 1/13 (7.7%; stenosis treated with surgical intervention) Length of stay Median stay 25 days (7-39 days)	Small number of patients, retrospective study design. Uneven sex distribution.

Study name,location, duration	Design and intervention(s)	Participants and setting	Outcomes	Results	EAC comments
Riss, Stift, Kienbacher (2010) Austria (six centres) 2006-2009	Retrospective Case series Endo-SPONGE. Sponges were changes at 2-3 days intervals. 1/20 had fibrin glue injection to improve healing, 1/20 has stent inserted for 7 days. Median follow-up was 17 months (1.5 to 29.8) Conflicts of interest not reported. Status of study: published. Endo-SPONGE ● No comparator ●	N=20 (13 males, 7 females). Median age was 66.3 years (range 54.8-91.2 years). 20/20 treated for rectal cancer (2/20 the upper third, 8/20 the middle third and 10/20 the lower third of the rectum). A protective stoma was created in 14/20. Neoadjuvant short-term radiotherapy in 1/20, long-term radio/chemotherapy in 5/20. Indication: 17/20 anastomotic leakage, 3/20 insufficiency of a rectal stump after Hartmann's procedure. Six surgical centres Inclusion criteria: consecutive patients who had undergone initially successful endo-sponge assisted treatment of anastomotic leakage following rectal cancer surgery (2006-2009) ●	Follow-up duration Time from primary operation to anastomotic leakage Mortality Complications Stoma reversal Duration of therapy ●	Mortality 0 related to Endo-SPONGE (5 unrelated) Stoma reversal Stoma reversal in 13/17 (76.5%) Time to completion Median duration of therapy was 21 days in groups of patients who did or did not develop an abscess Complications 1/20 of patients developed anal stenosis. 5/20 (25%) developed a recurrent symptomatic abscess (3/5 stage C, 1/5 stage B, 1/5 stage A)	Long term follow up of patients successfully treated with Endo-SPONGE (follow-up of the patient group in Riss et al. 2009). The EAC will only report the additional, unique outcomes from the long-term follow-up. Small number of patients. Lack of comparator Use of other non-operative interventions (fibrin glue, stent) Lack of conflicts of interest statement.

Study name,location, duration	Design and intervention(s)	Participants and setting	Outcomes	Results	EAC comments
Riss, Stift, Meier (2009) Austria (single centre) September 2007 to June 2008	Retrospective Case series Endo-SPONGE. Applied as primary therapy or if previous treatment options failed to achieve sufficient leak control. Antibiotics were administered in case of ongoing sepsis or peritonitis. Hospitalization was only necessary in case of replacement or poor general condition. Performed under general anesthesia or moderate sedation. Sponge changes every 2-3 days. One patient showed an early anastomotic dehiscence 7 days after LAR. In all other patients (n = 8), the median time from primary surgery (LAR or Hartmann) to anastomotic leakage was 2.5 month (range: 1–24). No follow-up time reported as this is only reporting on short-term treatment outcomes Conflict of interests not reported. Status of study: published. Endo-SPONGE ● No comparator ●	N=9 (5 males, 4 females). Median age 63.5 years (range 50-71). all n=9/9 had initial anterior resection due to low rectal cancer Indication: 6/9 anastomotic dehiscence following low anterior resection, 3/9 rectal stump insufficiency following Hartmann's procedure. 1/9 neoadjuvant short-term radiotherapy, 3/9 neoadjuvant chemoradiotherapy, 1/9 had liver metastasis. 2/9 received chemoradiotherapy after the index operation. 4/6 patients after low anterior resection had protective stoma. Single centre Inclusion criteria: patients who developed an abscess in the pelvis following an anterior resection of low rectal cancer (2007 – 2008) ●	Time to anastomotic leakage Total time of treatment Duration of Endo-SPONGE replacement Mortality Complications Treatment success QoL: patient's satisfaction, alteration in daily life activity, pain sensation Mortality ●	Overall Success 66.6% (6/9) successful leakage healing (cleaning and shrinking or wound, nearly closed and covered in granulation tissue) Mortality 0 related to Endo-SPONGE (1 unrelated) Time to completion Median total time of treatment was 3 weeks (2-8) Median duration of Endo-SPONGE replacement was 15 min (5-65) Quality of Life Median score for 'patient's satisfaction' was 3 (0-9), 'alteration in daily life activity' was 5 (1-9) and 'pain sensation' 3 (0-6) during the Endo-SPONGE treatment. 6/8 patients would undergo the treatment again, 2/8 would not.	Patients may overlap with Riss, Stift, Kienbacher (2010) therefore the EAC will only report the long term outcoems from Riss et al (2010) Small number of patients, retrospective study design, single centre. Lack of conflicts of interest statement. Some outcomes not presented separately for anastomotic leakage patients (n=9), rectal stump insufficiency n=3. Lack of detailed exclusion criteria.

Study name,location, duration	Design and intervention(s)	Participants and setting	Outcomes	Results	EAC comments
Rottoli (2018) Italy (single centre) March 2016 to March 2017	Prospective Case series Endo-SPONGE. The first application of the device was scheduled under deep sedation. Device was replaced every 48-72h.Antibiotic treatment was given at the time of diagnosis for at least 1 week and continues as long as necessary. Median follow was 11.6 months (6-18) after confirmation of healing of the anastomotic leak Authors declare no conflict of interests. Status of study: published. Endo-SPONGE ● No comparator ●	N=8. Median age was 37 years (18-59). Indication: 7/8 ulcerative colitis refractory to medical treatment, 1/8 familial adenomatous polyposis Single centre Inclusion criteria: patients with diagnosis of anastomotic leak (partial) after ileal pouch-anal anastomosis (IPAA); all leaks were symptomatic ad associated with signs of sepsis (March 2016 – March 2017) Exclusion criteria: a complete anastomotic dehiscence or active bleeding (either from the pouch or the presacral plane) requiring surgical intervention ●	Primary outcomes: The rate of successful healing at 6 months from the leak diagnosis Secondary outcomes: Operative time – not discussed Perioperative variables (time to anastomosis leakage diagnosis, time to Endo-SPONGE treatment and duration, hospital stay, ileostomy reversal, follow-up time, recurrence) The rate of intra- and postoperative complications The number of changes of the device before discharge ●	Overall success 100% (8/8) (cavity reduced in size and covered in granulation tissue) Stoma reversal Ileostomy was reversed in 7/8 at a median of 2.5 (1-6) months from the confirmation of healing Time to completion complete healing of the leak was documented after a median of 60 (24-90) days from the first treatment Number of sessions Endo-SPONGE treatment started at a median of 6.5 (1-15) days after diagnosis and lasted for a median of 12 (3-32 days) Device was replaced a median of 3 (1-10) times Complications No patients reported incontinence to faeces or gas Length of stay Median 15.5 days (6-48)	Small case series, single centre. Lack of baseline characteristics. Outcomes (operative time) not discussed

Study name,location, duration	Design and intervention(s)	Participants and setting	Outcomes	Results	EAC comments
Schiffmann (2019) Germany (single centre) November 2007 to March 2015	Comparative cohort study (retrospective) Endo-SPONGE with neoadjuvant (nRCT) (the treatment group) vs Endo-SPONGE without nRCT (the control group) An intensified nRCT (a daily intake of capecitabine with a single dose between 1000 and 1650 mg/m^2 combined with weekly applications of irinotecan (40 mg/m^2) or oxaliplatin, and local radiation 5 days a week with a single dose of 1.8 Gy adding up to 55.8 Gy. Endo-SPONGEs were changed every 3 days. Mean tumor distance from anal verge was 5.8 cm (2-10) in the treatment and 7.4 cm (4-11) in the control group (p=0.288). Follow up time not reported Authors declare no conflict of interest. Status of study: published. Endo-SPONGE + neoadjuvant radiochemotherapy Endo-SPONGE – neoadjuvant radiochemotherapy	Treatment group (Endo-SPONGEin patients receiving neoadjuvant radiochemotherapy): N=11 (10 males, 1 female). Mean age 66.1 years. Mean American Society of Anesthesiologists (ASA) score 2.36. Indication: 11/11 (100%) rectal cancer. Control group (Endo-SPONGE in patients not receiving radiochemotherapy): n=8 (7 males, 1 female). Mean age 62.4 years. Mean ASA score 2.13. Indication: 5/8 (62.5%) rectal cancer, 3/8 (37.5%) colon sigmoideum cancer. Single centre Inclusion criteria: patients treated with endoscopic vacuum therapy for anastomotic leakage after rectal resection for cancer with or without nRCT. There was an indication for nRCT for all patients with rectal cancer in the lower and middle rectum with a local cancer stage T3/4 or positive lymph nodes or both (November 2007 – March 2015)	Primary outcomes: Mortality Treatment success (healing of anastomotic leak) Long-term preservation of intestinal continuity (the absence of a stoma after 18 months) Secondary outcomes: Number of sponges needed Length of treatment Time until closing of protective ileostomy	Overall success Endo-SPONGE + neoadjuvant radiochemotherapy – 90.9% (10/11 versus Endo-SPONGE only - 100% (8/8) (p=0.381) Success definition not reported Mortality 0 related to Endo-SPONGE Stoma reversal/bowel continuity Long-term preservation of continuity was 63.6% (7/11) in nRCT group versus 62.5% (5/8) in Endo-Sponge only group (p=0.96) Time to completion Mean length of treatment was 31.1 days in nRCT group versus 15.9 days in Endo-Sponge only group (p=0.04). Number of sessions Mean number of sponges 9.6 in nRCT group versus 5 in Endo-Sponge only group (p=0.042)	Small number of patients, retrospective study design, single centre. Lack of exclusion criteria.

Study name,location, duration	Design and intervention(s)	Participants and setting	Outcomes	Results	EAC comments
Srinivasamurthy 2013 UK (single centre) September 2007 to May 2011	Retrospective Case series. Endo-SPONGE. Used according to the manufacturer's instructions; the sponge was changes under general anaesthetic with a flexible endoscope. Each patient had one sponge per application, with exception of one occasion of double sponge placement. Median time to leak detection 29 days (range 10-115) Median follow-up time 41 months (10-45) to report ileostomy reversal Median follow-up of 17 months to report recurrent abcesses Authors declare no conflict of interest. Status of study: published. Endo-SPONGE ● No comparator ●	N=8 (7 males, 1 female). Median age 66.5 years old (range 45-79). Anastomosis type: 6 low rectal, 1 colo-anal, 1 ileoanal. Short course radiotherapy used in 6, radical radiotherapy for previous bladder carcinoma in 1. Single centre Inclusion criteria: all patients who underwent Endo-SPONGE treatment for extraperitoneal pelvic anastomotic leakage in our hospital between September 2007 and May 2011. ●	Complete closure or reduction in the abscess cavity size Ileostomy reversalTime to stoma reversal Restoration of bowel continuity Number of sponges used Treatment period ●	Overall success Closure or reduction achieved in 75% (6/8) Stoma reversal/bowel continuity Ileostomy reversal in 5/8 (63%). Restoration of bowel continuity within or after 6 weeks of initial surgery in 4/5 (80%) and 1/3 (33%), respectively. Overall 62.5% (5/8). Time to completion Median treatment period: 26 days (range 7-49 days) Number of sessions Median number of sponge applications: 4 (range 1-7)	Small sample size, single centre. Uneven sex distribution. Lack of comparator.

Study name,location, duration	Design and intervention(s)	Participants and setting	Outcomes	Results	EAC comments
Strangio (2015) Italy (single centre) September 2008 to October 2013	Case series (not reported whether retrospective or prospective).. Endo-SPONGE. All patients received broad spectrum antibiotics. Single or multiple sponges inserted, a constant vacuum pressure of 150 mmHg was used. Sponges were changed every 48-72h. Changes done usually in conscious sedation with 5mg midazolam IV. Outpatient treatment after a few sponge exchanges. Median time to leak detection 17 days (range 0-102 days) Median follow-up of 9 months (5-12) for mortality Authors declare no conflicts of interest. Status of study: published. Endo-SPONGE ● No comparator ●	N=25 (18 males, 7 females). Mean age: 67 years (range 37–89). 19 underwent anterior rectal resection (18 rectal cancer, 1 rectal endometriotic nodule), 5 left colectomy (4 left-sided colon cancer, 1 acute diverticulitis) and 1 proctocolectomy for severe ulcerative colitis. For patients with colorectal resection, 8/22 had radiochemotherapy and 10/22 only chemotherapy. Median dimension of cavity was 56 mm (range 15-100mm).Anastomotic leak extended from 70 to 270 degrees and the median size of cavity was 56mm (range 15-100mm Single centre Inclusion criteria: consecutive patients presenting with anastomotic leakage following colorectal surgery, with or without protective stoma. Patients with clinical signs and symptoms suggesting an inflammatory complication confined in the pelvis (September 2008 – October 2013) Exclusion criteria: patients with signs of a generalized peritonitis or a complete anastomotic dehiscence. ●	Complete healing of anastomotic leakage Treatment failure requiring surgery Closure of protective ileostomy and restoration of bowel continuity Mortality Number of sponges used Time to Endo-SPONGE treatment ●	Overall success Complete healing in 88% (22/25) Mortality 0 related to Endo-SPONGE Stoma reversal/bowel continuity Closure of protective ileostomy and restoration of bowel continuity achieved in 11/13 (84.6%) of patients; 2 had definitive stoma Time to completion Median duration of 4 weeks (range 1-32) Number of sessions Median number of applications per patient was 9 (1-39) Complications 1 patient developed ileal fistula and underwent surgical re-intervention.	No comparator. Small case series, single centre. Possible overlap with Manta (2016).

Study name,location, duration	Design and intervention(s)	Participants and setting	Outcomes	Results	EAC comments
van Koperen (2009) The Netherlands (multicentre) July 2006 to April 2008	Case series (not reported whether retrospective or prospective) Endo-SPONGE. The sponge is changed every 3-4 days. In 6 patients general anesthesia was used, in 3 under a light sedation. 7 patients required no sedation. Median duration between the initial surgery and the discovery of the leakage was 11 days (range 3–150 days). Median follow-up after closure of the abscess cavity was 4 months (2-16) Authors declare no conflict of interests. Status of study: published. Endo-SPONGE ● No comparator ●	N=16 (9 males, 7 females). Median age of 64 years (19-78). Indication: 13/16 malignancy (rectal cancer), 3/16 benign (ulcerative colitis). 9/13 received radiotherapy, 2/13 chemoradiation. Mean anastomosis level was 5 cm (2-8) from anal verge. 8/16 had stoma created during primary surgery. Multicentre Inclusion criteria: patients with a presacral cavity after anastomotic leakage (July 2006 – April 2008) ●	Primary outcomes: closure of the cavity The ability to close the ileostomy and factors associated with successful closure Other outcomes: Time between the initial surgery and the discovery of the leakage Time between surgery and start sponge treatment Number of sponges placed initially (first insertion) Number of sponge replacements (overall) Complications/treatment failure Follow-up after the closure of the abscess cavity ●	Overall success Closure of the abscess cavity was successful in 9/16 (56%) patients Stoma Reversal Stoma reversal in 5/9 patients with closed abscess cavity. 2 on waiting list and 2 with definitive stoma. Time to completion Median of 40 days (28-90) Treatment sessions Median number of sponges initially places was 1 (1-3) Median amount of sponge replacements was 13 (8-17) Complications N=1 had bleeding in abscess cavity, N=1 had stopped treatment due to pain, n=1 stopped treatment due to insufficient cavity closure, n=2 had recurrent abscess	Small number of patients, retrospective design. Lack of detailed inclusion and exclusion criteria Some centres had only 1 patient

Wasmann (2019) The Netherlands (single centre) 2002-2017	Non-concurrent cohort study (retrospective). Endo-SPONGE. Sponges exchanged every 3 to 4 under light sedation days at the endoscopy room. Admission was not required; after discharge, outpatient appointments were made to change sponges. Transanal suture closure was performed. Anastomotic leak was detected between the 3rd and 17th day post surgery, mean 8.2 SD 3.6 days Overall median follow-up was 8 years (IQA 4-12) Median follow-up for Endo-SPONGE treatment was 4 years (IQR 3-6) Median follow-up for conventional management was 13 years (IQR 10-15) Authors declare some conflict of interests (speaker' fees for 3/8 of authors). Status of study: published. Endo-SPONGE + Surgical closure ● Comparator: passive approach by diversion with ileostomy and occasional drainage of the presacral abscess cavity with subsequent wait and-see approach	N=22 Patient treated with conventional management "(11 male, 11 female). Mean age at IPPA surgery was 34.68 (SD 12.98). Indication: 18/22 ulcerative colitis, 4/22 inflammatory bowel disease unclassified. ASA score 1 in 7/22, 2 in 14/22 and 3 in 1/22 N=18 (12 male, 6 female). Mean age at IPPA surgery was 40.56 (SD 14.48). Indication: 17/18 ulcerative colitis, 1/18 inflammatory bowel disease unclassified. ASA score 1 in 4/18, 2 in 14/18 Single centre Inclusion criteria: consecutive ulcerative colitis or inflammatory bowel disease unclassified patients who underwent IPAA and developed anastomotic leakage (January 2010 – October 2017 for Endo-SPONGE patients) Exclusion criteria: patients with indication for IPAA due to familial adenomatour polyposis, Crohn's disease or colorectal cancer, postoperative diagnosis of Crohn's disease in the pouch, redo-pouch surgery only in the study period, anastomotic leakage detected later than 3 months after IPAA surgery, leakage treatment strategies not in accordance with early surgical closure principles, a functioning IPAA of less than 1 year, cognitive inability to reply to the questionnaire, deceased during follow-up, and nonresponders to the questionnaire. ●	Primary and secondary (pouch failure) outcomes– not of interest ● Secondary outcomes: Treatment-specific details: number of sponge changes, number of Endo-SPONGEs used, duration of treatment ● Short-term results of Endo-SPONGE treatment: time from IPAA to anastomotic leakage diagnosis, time from diagnosis to starting treatment, anastomotic closure at 6 months, time from diagnosis to observed closure on imaging, complications within 90 days, time to ileostomy reversal ●	Overall success 100% (18/18) at 6 months for ESC group 66.7% (14/21) at 6 months for CM group p=0.01 Cavity clean without significant proximal pouch retraction Stoma reversal/bowel continuity Median time to stoma reversal was 4 months (IQR 3-6) for ESC group 4 months (IQR 3-13) for CM group P=0.43 Time to completion Median time to anastomotic closure 30 days (IQR 17-40) for ESC group 76 days (IQR 49 – 339) for CM group p <0.001 Number of sessions Mean number of Endo-SPONGE changes per person was 2.7 (SD 1.4), Number of Endo-SPONGE changes after discharge n=23/48 (47.9%)	The study intervention was Endo-Sponge followed by surgical closure. Small non-concurrent cohort study, single centre. Conflict of interest declared

Study name,location, duration	Design and intervention(s)	Participants and setting	Outcomes	Results	EAC comments
	•			Mean number of Endo-SPONGE used per person was 3.2 (SD 1.7) Complications Complications of anastomotic leakage treatment n=0 (0%) in ESC group 2 (9.1%) in CM group	

Weidenhagen (2008b): Germany (single centre) 2002-2004	Case series (retrospective). Endoscopic vacuum device (describe Endo-SPONGE without mentioning the device name). Sponges are changed every 28-72h. Mean height of the anastomosis was 5.3 cm (1-12cm) above the anal verge. The length of the cavity was between 2 and 20 cm (mean 7.4 ± 5.1). The initial management of all patients included intensive nutritional support and broad-spectrum antibiotics. Initial sponge insertion was done under sedation; later sedatives were used (2-5 mg of midazolam per session). Follow-up not reported Authors declare a conflict of interest. Status of study: published. Endo-SPONGE ● No comparator ●	N= 29 (24 male, 4 female). Mean age was 66.7 years (42-79). Indication: 22/29 rectal cancer, 3/29 rectosigmoidal cancer, 2/29 large rectal adenoma, 1/29 diverticulitis, 1/29 rectal infiltration of endometrial cancer. 9/29 received preoperative radiochemotherapy. 5/29 had diabetes, 1/29 had a chronic intake of oral steroids. Protecting stoma created in 21/29 (19/21 protecting ileostomies, 2/21 colostomies) after primary surgery, 4/29 had stoma created after the secondary procedure. Single centre Inclusion criteria: patients with an anastomotic leakage after (low) anterior resection (2002-2004) ●	Patient excluded from the treatment Time of the diagnosis The treatment duration The number of sessions Duration of hospital stay Complications The improvement of the systemic inflammatory response Healing success The incidence of stenosis Stoma closure rate and time to closure ICU stay ●	Overall success Definitive healing in 96.6% (28/29) Mortality 0 related to Endo-SPONGE Stoma reversal/bowel continuity Stoma was closed in 22/25. Time to closure was 168.9 ± 81.7 days (9-321 days). Time to completion total treatment duration was 34.4 ± 19.4 days (4-79 days) number of sessions total number of endoscopic sessions per patient was 11.4 ± 6.3 (1-27) For 25/29 therapy was continued as an ambulatory (outpatient) treatment Complications No major bleeding occurred, minor bleeding observed in some patients on removal of sponge. Length of stay Mean hospital stay 30.5±12.8 (range 10-69)	The conflict of interest between the authors and the company. Small number of patients, retrospective and observational study design, single centre. Imbalance in sex distribution. Lack of exclusion criteria.

Study name,location, duration	Design and intervention(s)	Participants and setting	Outcomes	Results	EAC comments
Abstracts					
Di Mitri (2010) (abstract only) Italy (single centre) January to October 2009	Case series. Endo-SPONGE. The sponge system was changed every 48-72h. Performed by experienced endoscopists and taking approximately 15 minutes. Conflicts of interest not reported. Status of study: abstract only. Endo-Sponge ● No comparator ●	N=5 (5 male). Mean age 51.6 years (range 32-67). Indication: severe ulcerative colitis 1/5, colorectal cancer 4/5. Chemo- or radiotherapy in 100% of cancer patients. Single centre Inclusion criteria: patients with diverting stoma, who underwent rectal resection for rectal cancer and severe ulcerative colitis (January 2009 – October 2009) ●	Number of sessions required Adverse event Stoma closure Symptomatic and leak recurrence ●	Overall success 3 pts achieved a significant improvement with cavity reduction <1 cm Symptomatic and leak recurrence in n=2/3 after a mean of 5.5 months form the stoma closure Stoma reversal N=3/3 had stoma closed Number of sessions N=1 required just one session. n=3 mean 6.3 sessions (range 6-15) and 30.3 days (range 20-50). N=1 stopped treatment after 6 sessions (20 days) due to adverse event Complications N=1 arterial bleed	Abstract only. Very small number of patients. Lack of exclusion criteria. Lack of conflicts of interest statement. Single centre.

Study name,location, duration	Design and intervention(s)	Participants and setting	Outcomes	Results	EAC comments
Martel (2018) Northern Ireland (single centre) November 2008 to January 2013	Case series. Endo-SPONGE. Conflicts of interest not reported. Status of study: abstract only. Endo-SPONGE ● No comparator ●	N=10 (8 male, 2 female). Median age 59 years old. Indication: anastomotic leaks following low anterior resection 7/10, symptomatic low pelvis cavities following ileal pouch excision 2/10 or a perforated low Hartmann's stump 1/10. Single centre Inclusion criteria: patients with anastomotic leaks or symptomatic low pelvis cavities (November 2008 – January 2013) ●	Time to treatment Median duration of treatment Number of sponge changes Adverse events Cavity closure ●	Overall success N=4 had definitive closure of cavity Time to completion Median duration of treatment was 28.5 days (8-40 days) Median number of sponge changes 7 (2-11 changes)	Small case series, single centre. No comparator. No detailed inclusion or exclusion criteria. Abstract only. Lack of conflicts of interest statement.
McAuley (2013) UK (single centre) January 2011 to March 2013	Case series. Endo-SPONGE. N=1 treated as outpatient, n=2 treated as inpatients. Conflicts of interest not reported. Status of study: abstract only. Endo-SPONGE ● No comparator ●	N=3 Single centre Inclusion criteria: patients complicated by a localised anastomotic leak following a laparoscopic low anterior resection (January 2011 – March 2013). ●	Number of sponge changes Cavity closure ●	N=2 almost complete cavity closure, n=1 a residual 2.5cm cavity Number of treatment sessions Mean number of sponge changes 9 (7-12)	Very small number of patients, single centre. No comparator. Lack of detailed exclusion and inclusion criteria. Lack of conflicts of interest statement.

Appendix C – GRADE Assessment

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Overall Success Rate (follow up: range 2 months to 84 months)									
21	observational studies	serious [a,b]	serious [c]	serious [d]	serious [b]	none	Overall success rate was reported for 18 studies and 3 abstracts (including one comparative study (Schiffmann et al. 2019) and one study in patients with IAAP (Wasmann et al. 2019)). It is important to note that the definition of success varied across the studies. Pooled result from 21 studies was 279/328 (85%) but the range from the individual studies was 40% to 100%. One study (Schiffmann et al. 2019) compared outcomes in patients who received neo-adjuvant radiochemotherapy with patients who did not. The overall success rate in this study was 94.7% (18/19 patients) with no significant difference observed between patients who received neo-adjuvant radiochemotherapy (10/11) or no neo-adjuvant radiochemotherapy (8/8). One study (Wasmann et al. 2019) reported a success rate of 100% (18/18) but this was in patients with IAAP which may not be a relevant patient group.	⨁◯◯◯ VERY LOW	
Stoma/Ileostomy reversal/Bowel continuity restored (follow up: range 3 months to 84 months)									

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
15	observational studies	serious [e]	not serious	serious [d]	serious [b]	none	Fifteen studies (including one abstract) reported on the reversal or stomas and ileostomies, restoration of bowel continuity and preservation of bowel continuity. Pooled result from 14 studies was 144/188 (76.59%) but the range from individual studies was 38.4% to 92%. One study (Schiffmann et al. 2019) reported the long-term preservation of continuity in patients with and without neo-adjuvant radiochemotherapy; overall preservation of bowel continuity was 63.1% for the whole cohort (63.6% with neo-adjuvant radiochemotherapy and 62.5% without.	⨁◯◯◯ VERY LOW	

Number of treatment sessions (follow up: range 2 months to 64 months)

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
19	observational studies	serious [f]	serious [g]	serious [d]	not serious [h]	none	In total, 19 studies (including 3 abstracts) reported the number or treatment session but the number of treatment sessions was variably reported as a mean, a median or a range across individual studies. Across the 19 studies, the number of treatment sessions ranged from 1 to 57 sessions. From 8 studies, the median number of treatment sessions ranged from 3 (1-10) to 8 (1-18) while from 8 studies the mean number of treatment sessions ranged from 2.2 to 18.6 sessions. One study (Schiffman et al. 2019) reported a mean number of sponges of 7.7 for the whole cohort with a mean number of sponges in the neo-adjuvant radiochemotherapy group of 9.6 compared with 5 in the no neo-adjuvant radiochemotherapy group. It is important to note that the individual studies do not always provide a clear definition of a treatment session with some studies reporting a number of sponge insertions/applications (Katz et al. 2018; Keskin et al. 2015; Kuehn et al. 2016; Milito et al. 2017; Rottoli et al. 2018; Srinivasamurthy et al. 2013; Strangio et al. 2015; van Koperan et al. 2019; Wasmann et al. 2019; Martel et al. 2018; McAuley et al. 2013) while other studies reported the number of treatment sessions (Arezzo et al. 2015; Boschetti et al. 2018; Jimenez Rodriguez et al. 2018; Musetto et al. 2017; Nerup et al. 2013; Weidenhagen et al. 2008 and DiMitri et al. 2010).	⨁◯◯◯ VERY LOW	

Treatment Duration (follow up: range 1.5 months to 29.8 months)

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
15	observational studies	serious [i]	not serious [j]	serious [d]	not serious	none	In total, 15 studies (including 1 abstract) reported on the length of treatment (Arezzo et al. 2015; Boschetti et al. 2019; Jiminez-Rodriguez et al. 2018; Kuehn et al 2016; Nerup et al. 2013; Riss et al. 2010; Riss et al. 2009; Rottoli et al 2018; Schiffmann et al 2019; Srinivasamurthy et al 2013; Strangio et al 2015; van Koperan et al 2009; Wasmann et al. 2019; Weidenhagen et al 2008; Martel et al. 2018). Treatment duration was reported as duration of Endo-SPONGE therapy or as time to complete healing across the individual studies. The outcome was variably reported as a mean or median with ranges. One study did not report a total treatment duration but did report length of stay and follow up treatment separately (Nerup 2013).	⊕◯◯◯ VERY LOW	
Length of Hospital Stay									
3	observational studies	serious [i]	serious [k]	serious [d]	not serious [l]	none	Length of stay was reported as a mean and SD in one study (Weidenhagen 2008) and as a median in the remaining two (Nerup 2013 and Rottoli 2018). All studies reported the range in days and for length of stay the range was 6-69 days.	⊕◯◯◯ VERY LOW	
Mortality									

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
10	observational studies	serious [i]	not serious	not serious	not serious	none	In total, 10 studies (including 1 abstract) reported mortality. None of the studies reported mortality associated with endo-SPONGE treatment specifically. Four studies (Nerup et al. 2013; Schiffmann et al. 2019; Strangio et al. 2015; DiMitri et al. 2010) reported no deaths related to Endo-SPONGE but did not specify whether there were any unrelated deaths. Deaths considered to be unrelated to Endo-SPONGE were reported in six studies. One study (Jimenez-Reodriguez et al. 2018) reported 3 deaths not related to Endo-SPONGE (local recurrence, pneumococcal infection, bowel obstruction secondary to frozen pelvis), one study (Mussetto et al. 2017) reported 2 unrelated deaths (prostate cancer, metastatic cancer), one study (Riss et al. 2009) reported 1 unrelated death (heart attack) and one study (Riss et al 2010) reported 5 unrelated deaths (tumour progression and liver cirrhosis), one study (Keskin et al. 2015) reported 3 unrelated deaths and one study (Huismann et al. 2019) reported 1 unrelated death. Other studies did not explicitly report whether there were any deaths during the study period (related or unrelated).	⨁◯◯◯ VERY LOW	

Complications

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
11	observational studies	serious [i]	not serious	serious [d]	not serious	none	One study (Boschetti 2018) reported a colon perforation in one patients as a result of trying to increase the fistula size to accommodate endo-SPONGE. One study (Huisman 2019) reported 3 chronic sinus. Three studies (Mussetto 2017, Nerup 2013, Riss 2010)) reported stenosis in a total of 4 patients. Two studies (Riss 2010 and van Koperan 2009) reported recurrent symptomatic abscess in a total of 7 patients and one study (van Koperan 2009) reported bleeding in the abscess cavity. One study (Strangio 2015) reported that 1 patient developed ileal fistula and underwent surgical re-intervention. Three studies (Jimenez-Rodriguez 2018, Milito 2017, Wasmann 2019) reported no complications during treatment while one study (Weidenhagen 2008) reported minor bleeding in some patients.	⊕◯◯◯ VERY LOW	
Health Related Quality of Life									
2	observational studies	serious [i]	serious [m]	serious [d]	serious [m]	none	One study (Riss 2009 reported that 6/8 patients would undergo treatment with Endo-SPONGE again. One study (Arezzo 2015) reported 3 patients had a minor LARS score and 10 patients had a major LARS score.	⊕◯◯◯ VERY LOW	

Explanations

a. N=20 Non comparative, retrospective case series; N=1 non-matched comparative study (not randomised).
b. All studies have small sample sizes (range 3-34 patients)
c. Reported success rate ranged from 56% to 100% however success was defined differently across studies
d. While most of the studies use Endo-SPONGE, without a direct comparator it is difficult to assess the relative effect of Endo-SPONGE compared with standard care
e. Non comparative case series studies , reporting of outcome varies between reporting rate of stoma/ileostomy reversal, time to stoma ileostomy reversal, restoration of bowel continuity, and preservation of bowel continuity
f. The outcome is not clearly defined in the studies. It is not clear whether the number of treatment sessions/exchanges equates to the number of sponges used in each session. Some studies report the number of sponges and not the number of treatment sessions.

g. Number of sessions ranges from 2.2 to 13 across individual studies but these are variably reported as means, medians and counts.
h. It is unlikely that reporting of this outcome is imprecise in individual studies as the number of sessions/exchanges or sponges used is a simple count however care should when comparing this outcome across studies (see inconsistency)
i. Non comparative case series studies, small sample sizes
j. Reported time to healing ranged between a median 21 to 60 days. Some studies reported mean time to healing.
k. Reported as a median in two studies and a mean in one study. Mean length of hospital stay indicates a much higher possible length of stay.
l. Unlikely to be imprecise as this is a simple count for length of stay however care should be taken when comparing across studies (see inconsistency)
m. Only two studies report any HRQoL outcomes and they both report differently - one reporting LARS score and one reporting patient satisfaction

Appendix D - Model Testing

Scenario	Cost of Endo-SPONGE over percutaneous drain (Year 1)	Savings OP (Year 1)	Saving permanent stoma (Year 1)	Annual Budget Impact (Year 1)	Notes
Base case	£237,185.73	-£447,733.82	-£51,447.80	-£261,995.90	Endo-SPONGE, when compared to current treatment (percutaneous drain), is cost-saving over one year.
The number of patients equal to 0.	£0.00	£0.00	£0.00	£0.00	As expected.
The number of patients equal to 1000.	£2,371,857.31	-£4,477,338.25	-£514,478.03	-£2,619,958.96	As expected.
Patients non OP stage 1 to 0% in Endo-SPONGE	£0.00	-£543,229.15	-£95,726.65	-£638,955.80	There is no cost associated with using Endo-SPONGE and the patients are lost in the model; all the rest of OP patients are still in the system. In the model, greater number of OP patients will be saved by the intervention, thus, greatest 'savings OP'. In the model, more permanent stoma will be saved with Endo-SPONGE (due to lower number of patients with non-reversed stoma in Endo-SPONGE), thus,

					higher savings in ‘saving permanent stoma’. *The model is not robust.*
Patients non OP stage 1 to 0% in current process	£237,185.73	-£218,103.74	-£51,447.80	-£32,365.81	The cost for Endo-SPONGE stays the same; the patients from non OP in current process are lost in the model. Less OP patients in current process leads to less ‘savings OP’.
Cost of re-operation equal to £0.	£237,185.73	£0.00	-£51,447.80	£185,737.93	There is no savings associated with saving OP patients with Endo-SPONGE; Endo-SPONGE becomes cost incurring. As expected.
Cost of re-operation equal to £5,224.636.	£237,185.73	-£185,737.90	-£51,447.80	£0.03	Changing the cost of re-operation to £5,224.636 leads to Endo-SPONGE being cost neutral, but only during the first year. For subsequent years, the cost of annual stoma care leads to Endo-SPONGE being cost-saving.

Success rate for Endo-SPONGE to 0%.	£237,185.73	-£447,733.82	-£51,447.80	-£261,995.90	The success rate is not used anywhere in the model, thus, no changes in total costs. *The variable should be included in calculations.*
Success rate of current non OP to 0%.	£237,185.73	-£447,733.82	-£51,447.80	-£261,995.90	The success rate is not used anywhere in the model, thus, no changes in total costs. *The variable should be included in calculations.*
Stoma reversal rate for Endo-SPONGE to 0%.	£237,185.73	-£447,733.82	-£51,447.80	-£261,995.90	The value has an impact on number of patients with stoma reversed which is not used in any other calculations – no impact on costs. *The variable should be included in calculations.*
Stoma reversal rate for current process to 0%.	£237,185.73	-£447,733.82	-£51,447.80	-£261,995.90	The value has an impact on number of patients with stoma reversed, but it is not used in any other calculations – no impact on costs. *The variable should be included in calculations.*
Annual cost of stoma care/t to £0.	£237,185.73	-£447,733.82	£0.00	-£210,548.09	Setting the annual cost of stoma care/pt to £0 leads to no cost saving for Endo-SPONGE with regards to permanent stoma care. Endo-

					SPONGE is still cost saving.
In bed cost for Endo-SPONGE to £0.	£237,185.73	-£447,733.82	-£51,447.80	-£261,995.90	The costs are not included anywhere in calculations, thus, no impact on overall costs. Endo-SPONGE is still cost-saving. *The variable should be included in calculations.*
Weighted mean number of Endo-SPONGE per treatment course to 1.	-£27,237.06	-£447,733.82	-£51,447.80	-£526,418.69	There would be no cost of Endo-SPONGE treatment over percutaneous drain, thus, higher cost savings.
Weighted mean number of Endo-SPONGE per treatment course to 20.32.	£499,427.72	-£447,733.82	-£51,447.80	£246.09	The costs of Endo-SPONGE treatment over percutaneous drain will be much higher than base case. At 20.32 changes Endo-SPONGE will be cost incurring.
Endo-SPONGE price per pack of 10 to £100.	£237,185.73	-£447,733.82	-£51,447.80	-£261,995.90	There is no change of costs – the total cost to insert Endo-SPONGE is not calculated based on the costs of treatment and bottles provided. *The variable should be used in calculations.*

Endo-SPONGE price per pack of 10 to £5000.	£237,185.73	-£447,733.82	-£51,447.80	-£261,995.90	There is no change of costs – the total cost to insert Endo-SPONGE is not calculated based on the costs of treatment and bottles provided. *The variable should be used in calculations.*

Appendix E – EAC Model Changes

Change	Description	Cost difference at 1 year (no discount)	Cost difference at 10 years (3.5% discounting, no mortality)	Impact
Submission			-£4,935,110.08	
Single patient		-£2,619.96	-£7,250.26	
Correct calculation	Cannot apply difference in procedure costs to Endo-SPONGE patients where different proportion non-operative in each arm	-£2,419.52	-£7,049.82	Small reduction in cost saving
Discounting for 10 year model		-£2,419.52	-£6,183.75	Small reduction in cost saving
Theatre time & cost		-£2,110.76	-£5,892.39	Small reduction in cost saving
Remove staff costs		-£1,901.94	-£5,666.18	Small reduction in cost saving
Op/non-op rates	Set at 62.8% for both	-£502.45	-£3,994.23	Large reduction in cost saving
Success rates	Set at 85% for Endo-SPONGE and 70% for PD	£589.30	-£2,902.49	Large reduction in cost saving, becoming cost incurring in 1st year
Stoma reversal rates	Set at 77% for Endo-SPONGE, 62% for PD, 52% for operative	£773.15	-£1,373.44	Moderate increase in 1st year costs, small decrease in 10 year cost saving
EAC Scenario 1b:				
EAC theatre costing		£968.77	-£1,177.82	
EAC endosponge costing and percutaneous drainage costing		£1,141.10	-£1,005.49	Large increase in 1st year costs, moderate decrease in 10 year cost saving
SCENARIO2b				
Endo-SPONGE subsequent procedures in theatre	Set Endo-SPONGE procedure as £739.21	£4,427.34	£2,280.75	Large increase in costs for 1 and 10 year. No longer cost saving for either
SCENARIO3b				
Endo-SPONGE patients also receive percutaneous drainage	Total cost of PD procedures added to Endo-SPONGE costs (+ £1575.85)	£2,130.73	-£15.85	Moderate increase in costs for 1y and decrease in cost saving for 10 year. Approx cost neutral at 10 years.

Appendix F – Sensitivity Analysis

Variable	BASE CASE	Low Value	LV Source	High Value	HV Source
Cost of 1st procedure, Endo-SPONGE	£300.25	£108.00	NHS Ref costs 2018/19, outpatients FF33B, gen surgery/col surgery	£739.21	NHS Ref costs 2018/19, day case, FE01Z, FE02x, FE03x
Cost of subsequent procedures, Endo-SPONGE	£199.74	£108.00	NHS Ref costs 2018/19, outpatients FF33B, gen surgery/col surgery	£739.21	NHS Ref costs 2018/19, day case, FE01Z, FE02x, FE03x
Cost of Endo-SPONGE	£271.11	£216.89	-20%	£325.33	+20%
Number of Sponges / procedures	10.7	1	EAC interpretation of evidence synthesis	18	EAC interpretation of evidence synthesis +20%
Cost of 1st PD procedure	£400.33	£119.00	NHS Ref costs 2018/19, outpatients FF53A, Interventional radiology	£1,314.00	NHS Ref costs 2018/19, outpatients YF04C, Interventional radiology
Cost of subsequent procedures, PD	£291.05	£119.00	NHS Ref costs 2018/19, outpatients FF53A, Interventional radiology	£1,314.00	NHS Ref costs 2018/19, outpatients YF04C, Interventional radiology
Cost of PD equipment	[redacted]	[redacted]	-20%	[redacted]	+20%
number of PD procedures	4.4	3.5	-20%	5.2	+20%
cost of surgery	£8,523.68	£6,818.94	-20%	£12,500.00	Company submission
% Non-operative, Endo-SPONGE	62.80%	28.75%	EAC interpretation of evidence synthesis	100.00%	EAC interpretation of evidence synthesis
% Non-operative, comparator	62.80%	28.75%	EAC interpretation of evidence synthesis	100.00%	EAC interpretation of evidence synthesis
Endo-SPONGE success rate	85.00%	40.00%	EAC interpretation of evidence synthesis	100.00%	EAC interpretation of evidence synthesis
PD, success rate	70.00%	29.00%	EAC interpretation of evidence synthesis	82.00%	EAC interpretation of evidence synthesis
Permanent stoma rate surgery	52.00%	41.60%	-20%	62.40%	+20%
Permanent stoma rate Endo-SPONGE	77.00%	38.00%	EAC interpretation of evidence synthesis	92.00%	EAC interpretation of evidence synthesis
Permanent stoma rate PD	62.00%	50.00%	EAC interpretation of evidence synthesis	94.00%	EAC interpretation of evidence synthesis
Annual cost of stoma	[redacted]	[redacted]	Inflated cost from HTA (actually less than 20%)	[redacted]	+20%

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology guidance

Assessment report overview

Endo-SPONGE for treating colorectal anastomotic leakage

This assessment report overview has been prepared by the Medical Technologies Evaluation Programme team to highlight the significant findings of the External Assessment Centre (EAC) report. It includes **brief** descriptions of the key features of the evidence base and the cost analysis, any additional analysis carried out, and additional information, uncertainties and key issues the Committee may wish to discuss. It should be read along with the company submission of evidence and with the EAC assessment report. The overview forms part of the information received by the Medical Technologies Advisory Committee when it develops its recommendations on the technology.

Key issues for consideration by the Committee are described in section 6, following the brief summaries of the clinical and cost evidence.

This report contains information that has been supplied in confidence and will be redacted before publication. This information is highlighted in yellow. This overview also contains:

- Appendix A: Sources of evidence
- Appendix B: Comments from professional bodies
- Appendix C: Comments from patient organisations
- Appendix D: Decision problem from scope

1 The technology

Endo-SPONGE (B. Braun) is a minimally invasive treatment for anastomotic leakage in the low colorectal area after colorectal surgery. The Endo-SPONGE system uses vacuum therapy, which is commonly used for the treatment of chronic and complex wounds.

The Endo-SPONGE system consists of an open pore sponge with a Redon drain, a sponge pusher, silicon overtube guides and a drainage set and system. It is designed to be used in conjunction with the Redyrob Trans Plus drainage bottle (B.Braun).

The sponge is inserted into the leakage cavity using a flexible endoscope or through open access via the anus. A drainage tube is connected to the sponge at one end and a drainage bottle at the other end. The bottle is a low-vacuum drainage container and exerts suction to provide continuous and constant negative pressure in the sponge. The number of sponges needed for completing treatment varies, ranging from 1 to 39. The sponge is changed every 24 to 72 hours. Sedation and analgesia may be needed for the insertion procedure. Some potential risks associated with Endo-SPONGE are residual sponge particles, erosion of structures adjacent to sponge and injury to intestinal wall and bleeding.

The Endo-SPONGE system is not suitable when the following conditions are present:, malignant tumour wound; necrotic tissue/gangrene; untreated osteomyelitis; anastomotic leakage directly adjacent to vessels; bladder or small bowels obstruction, non-drainable septic focus, systemic sepsis and clotting disorders.

2 Proposed use of the technology

2.1 Disease or condition

Anastomotic leakage refers to the escape of luminal bowel contents through a surgically created junction between two sections of bowel (McDermott et al., 2016). It is one of the most serious complications after colorectal surgery. Low

anterior resections are associated with a leakage rate ranging from 3% to 24% (Kirchoff et al., 2010). Anastomotic leakage is associated with increased morbidity and mortality rates and can result in delayed wound healing, extended hospital stays and the need for a stoma (Clow et al., 2009, den Dulk et al., 2007). Anastomotic leakage also increases the need for reoperation, the risk of cancer recurrence and reduces both overall and disease free survival (Mirmezami et al., 2011).

2.2 Patient group

The Endo-SPONGE system is intended for treating anastomotic leakage after colorectal surgery. In the UK, an analysis of the Hospital Episode Statistics database found that the rate of anastomotic leak following colorectal surgery was 6.4% between 2007 and 2011, and that anastomotic leakage was associated with higher rates of hospital mortality, 30-day readmission, and post-operative infection compared with no anastomotic leakage after colorectal surgeries (Wan et al., 2014). Risk factors for anastomotic leakage can be broadly associated with patient and procedure related factors. Patient-related factors include male gender, smoking, steroid use and nutritional status. Procedure-related factors include longer operation time (i.e. longer than two hours), multiple blood transfusions, intraoperative contamination, and increased urgency of the operation (Khan et al., 2007).

2.3 Current management

NICE has not published guidelines on the treatment of colorectal anastomotic leakage. Guidance from the Association of Surgeons of Great Britain and Ireland on Prevention, Diagnosis and Management of Colorectal Anastomotic Leakage (March 2016) states that people with anastomotic leakage who are considered clinically stable may be treated conservatively using fluids, antibiotics and oxygen, with close clinical observation. However, for people showing signs of sepsis, steps must be taken to remove the source of the leak within 3 to 18 hours, depending on the underlying condition and severity of infection. In less severe cases of sepsis associated with extraperitoneal rectal anastomotic leakage, proximal defunctioning of the anastomosis with transanal or transperitoneal drainage may be considered. If there is

radiological evidence that the anastomotic cavity is separate from the bowel, or if there are multiple sites of anastomotic leakage, surgical intervention is needed.

2.4 Proposed management with new technology

The Endo-SPONGE is intended to be used for the treatment of anastomotic leakage in the low colorectal area after colorectal surgery, where the leak has created a drainable cavity.

3 Company claimed benefits and the decision problem

The main claimed benefits and decision problem from the scope are attached as Appendix C.

No variation was made to the final scope.

4 The evidence

4.1 Summary of evidence of clinical benefit

The company identified 21 relevant publications from a literature search. The submission included 3 published systematic reviews (Clifford et al, 2019, Shalaby, 2019 and Popivanov, 2019). The other 18 studies included 7 prospective non-comparative studies and 11 retrospective non-comparative studies.

The EAC included 20 studies including 18 non-comparative studies described in the company submission and also included 2 comparative observational studies (Schiffmann et al, 2019 and Wasmann et al, 2019). The EAC excluded the 3 systematic reviews because they were of low quality and it preferred to use the source studies. The EAC also included 3 abstracts (DiMitri et al. 2010; Martel et al. 2013; and McAuley et al. 2013) in the assessment report. One UK study (Srinivasamurthy et al, 2013) was included, and most other studies were done in European countries including Austria, Demark, France, Germany, Italy, Netherlands, Spain and Turkey. The rationale for the study

selection is described in the table in the appendix A of the assessment report (page 126).

Details of the included studies are summarised in Table 1 (page 11). The EAC critically appraised the evidence and concluded that the quality of these studies is very low because many studies had a retrospective design, no comparator and small sample sizes. All studies were small with sizes ranging from 3 (McAuley et al. 2013) to 34 people (Weidenhagen et al. 2008). The EAC indicated that the small number of patients in each study could be reflective of low incidence of anastomotic leakage after colorectal surgery.

Length of follow-up was not consistently defined across the studies and it was reported variably as a mean, median or minimum making it difficult to compare across studies. The EAC considered that the wide variation reported in the studies regarding population characteristics, time to treatment, concurrent or additional treatments may reflect the clinical uncertainty and variation in practice when treating people with anastomotic leakage. Clinical experts have noted that there is no standard clinical protocol for anastomotic leak treatment.

Results from the individual studies are presented in Table 1 (see below). Pooled results of outcomes of interest are reported as following:

- Success rate was reported in 21 studies including 3 abstracts. The EAC noted that the definition of success varied across the studies (the definition of the individual studies was in the table 1 in the assessment report, page 11). Most frequently studies defined successful treatment as closure of cavity to less than1cm or as a reduction of cavity with complete granulation. The pooled result suggested 85.0% of anastomotic leakage were successful, ranging from 40% to 100%.
- The reversal of stomas and ileostomies, restoration of bowel continuity and preservation of bowel continuity were reported in 15 studies including 1 abstract. Pooled results from 14 studies reporting the reversal of stoma or ileostomy was 76.6% (144/188), ranging from 38.5% to 92.3%.

- Complications were reported in 12 studies including 1 abstract and covered colon perforation, chronic sinus; stenosis, recurrent symptomatic abscess reported, bleeding in the abscess cavity, minor bleeding, arterial bleeding and ileal fistula developed and underwent surgical re-intervention. Three studies (Jimenez-Rodriguez et al, 2018, Milito et al, 2017, Wasmann et al, 2019) reported no complications during treatment.
- Mortality was reported in 10 studies including 1 abstract. None of these studies reported mortality associated with endo-SPONGE treatment specifically.
- The number or treatment sessions was reported in 19 studies including 3 abstracts. The number of treatment sessions ranged from 1 to 57 sessions and the EAC noted that a treatment session was not clearly defined for instance, some studies reported number of sponge insertions/applications and other studies reported the number of treatment sessions.
- Duration of treatment was reported in 15 studies including 1 abstract. Treatment duration was reported as time to complete healing (n=7 studies) or as duration of Endo-SPONGE therapy (n=7). Six studies reported time to stoma reversal. The outcome was variably reported as a mean or median with ranges.
  - Median time to complete healing ranged from 40 to 60 days.
  - Median time to stoma reversal varied across the individual studies in terms of when time to reversal assessed and how it was reported. Median time from initial surgical resection to stoma reversal was 10 months (Huisman et al., 2019). Median time to stoma reversal from healing of 2 months (1-6) and 4 months (IQR 3-6) respectively (Rottoli et al., 2018; Wasmann et al., 2019). One study (Weidenhagen et al., 2018) reported that stoma reversal occurred after 168 (SD 81.7) days.
  - Median Endo SPONGE treatment duration ranged between 21 and 28 days but the number of treatment days ranged from 1 to 109 days. Total treatment duration was 34.4 ± 19.4 days (4 to 79 days) in Weidenhagen et al. (2008).
- Length of hospital stay was reported in 3 studies, ranging from 6 to 69 days. Mean length of stay was 30.5±12.8 days in one study (Weidenhagen

et al, 2008) while median length of stay was 15.5 days (Rottoli et al, 2018) and 25 days (Nerup et al, 2013).

- Patient outcomes were reported in 2 studies. Patient acceptability was high with 75% (6 of 8) patients would undergo Endo-SPONGE treatment again if necessary (Riss et al, 2009). Functional bowel outcome was measured using the low anterior resection syndrome score (LARS) questionnaire in 1 study (Huismann et al, 2019). The median LARS score in the Endo-SPONGE group was 37 (23–42, n=13) points and 30 (4–41, n=21) points in the control group (P = 0.009) (lower score relates to better quality of life). The control group used were 21 patients who did not have anastomotic leak following surgery.

The EAC considered that the clinical evidence suggests that Endo-SPONGE could be a treatment option for anastomotic leaks and may reduce the need for further surgery; however, the evidence is very low quality, variable and inconsistent. The EAC noted that Endo-SPONGE was used with antibiotics in 6 studies so the evidence does not support its use as a replacement to antibiotics. The EAC suggested that Endo-SPONGE may be considered as an alternative to percutaneous drainage for treating anastomotic leakage before surgical interventions to reduce the need for patients with anastomotic leak to undergo further surgery. One study (Wasmann et al, 2019) indicated that the use of Endo-SPONGE before a planned surgical closure was associated with significantly more anastomotic closures in a shorter period of time compared with conventional management in (100% closure after a median of 30 days versus 67% closure after a median of 76 days). The EAC concluded that the treatment decision to use Endo-SPONGE should be on the basis of a clinical assessment and discussion between clinicians and patients taken into account of factors such as severity of leak, patient condition, and patient preference.

Table 1: Summary of studies (full text) assessed by the EAC.

Study and design, location	Participants/ population	Intervention & comparator	Outcome measures	Results	EAC comments
Schiffmann (2019) Comparative cohort study Germany (single centre)	Patients treated with endoscopic vacuum therapy for anastomotic leakage after rectal resection for cancer with or without neoadjuvant radio-chemotherapy (nRCT). Inclusion criteria: patients treated with endoscopic vacuum therapy for anastomotic leakage after rectal resection for cancer with or without nRCT. There was an indication for nRCT for all patients with rectal cancer in the lower and middle rectum with a local cancer stage T3/4 or positive lymph nodes or both (November 2007 – March 2015	Treatment group (EndoSPONGE with neoadjuvant radio-chemotherapy): n=11 (10 males, 1 female). Mean age 66.1 years. Mean American Society of Anesthesiologists (ASA) score 2.36. Indication: 11/11 (100%) rectal cancer. Control group (EndoSPONGE with neoadjuvant radio-chemotherapy): n=8 (7 males, 1 female). Mean age 62.4 years. Mean ASA score 2.13. Indication: 5/8 (62.5%) rectal cancer, 3/8 (37.5%) colon sigmoideum cancer	Primary outcomes: • Mortality • Treatment success (healing of anastomotic leak) • Long-term preservation of intestinal continuity (the absence of a stoma after 18 months) Secondary outcomes: • Number of sponges needed • Length of treatment • Time until closing of protective ileostomy	There were no significant differences in patient characteristics between both groups. Success rate, Overall: 94.7% EVT after nRCT: 90.9% EVT without nRCT: 100% P=0.381 Mortality There was no death reported during the study period. Long term preservation of continuity, Overall: 63.2%. EVT after nRCT: 63.6% EVT without nRCT: 62.5% P=0.960 Number of sponges needed, Overall: 7.7 EVT after nRCT: 9.6 EVT without nRCT: 5.0 P=0.042 Length of treatment (days), Overall: 24.7 EVT after nRCT: 31.1 EVT without nRCT: 15.9 P=0.040 Time until closing of protective ileostomy (months), Overall: 10.2 EVT after nRCT: 8.4 EVT without nRCT: 12.8 P=0.148	Small number of patients, retrospective study design, single centre. Lack of exclusion criteria.

Wasmann (2019) Comparative cohort study, Netherlands (single centre)	Patients with an anastomotic leakage after IPAAwith ileal pouchanal anastomosis (IPAA). Anastomotic leakage was confirmed either by radiological imaging or during surgical exploration within 90 days following IPAA surgery. Inclusion criteria: consecutive ulcerative colitis or inflammatory bowel disease unclassified patients who underwent IPAA and developed anastomotic leakage (January 2010 – October 2017 for EndoSPONGE patients) The overall median time of follow-up was 8 years [IQR 4–12].	Intervention: EndoSPONGE. When the cavity was clean without significant proximal pouch retraction, transanal suture closure was performed under general anaesthesia in a short hospital admittance. Comparator: Conventional management included diversion combined with transabdominal, transgluteal, or transanal drainage of the presacral abscess cavity. A wait-and-see policy was adopted and progress of anastomotic healing was regularly checked by either contrast enema	The primary outcome was pouch function which was measured with the validated pouch dysfunction questionnaire. Secondary outcomes • pouch failure, • treatment-specific details (i.e. type of CM drainage, the number of Endo-sponge changes) • Treatment specific details included time from IPAA to anastomotic leakage diagnosis, time from diagnosis to starting treatment, anastomotic closure at 6 months [chronic pelvic sepsis], time from diagnosis to observed closure on imaging, complications of anastomotic leakage treatment within 90 days, and time to ileostomy reversal.	18 patients had AL after IPAA treated with Endosponge (ESC) and 22 patients treated with conventional management (CM). Median follow-up time: ESC: 4 years [IQR 3–6] CM:13 years [IQR 10–15], P <0.001 Mean number of Endo-sponge changes per patient=2.7 (SD=1.40). Mean number of Endo-sponge used per patient= 3.2 (SD=1.7) Median time to Endo-sponge treatment [days]=11, (IQR, 5 to 15. Number of complications: ESC=0; CM=2 (9.1%); P=NA Median time to diagnosis, days: ESC=9, IQR 7 to13 CM=8, IQR 6 to 17 P=0.87 Median time until AL closure, days: ESC=30, IQR 17 to 40 CM=76, IQR 49 to 339 P<0.001 Median time to stoma reversal, months: ESC=4, IQR 3 to 6 CM=4, IQR 3 to 13 P=0.43.	The study intervention was Endo-Sponge followed by surgical closure. Small non-concurrent cohort study, single centre. Conflict of interest declared

Jiménez Rodríguez (2018) Prospective non-comparative study; Spain (single centre)	Patients scheduled to undergo VAC therapy for dehiscence of lower colorectal anastomosis or opening of the rectal stump after anterior resection for rectal cancer were prospectively included in this study. Patients with severe signs of systemic inflammatory response that needed immediate intensive treatment were not included because they received an urgent surgical treatment. The mean follow-up period after cavity closure was 12.36 ± 7.9 months.	Intervention: EndoSPONGE. Depending on size of cavity 2 or more were used. Initially pressure of 375 mmHg was used and modified to 150 mm Hg at the first sponge replacement, sponges were changed every 3 – 5 days. In all patients, the first treatment was performed in-hospital, but the successive replacements were carried out on an outpatient basis for 11 patients. For 10 patients fibrin glue was used in addition after VAC therapy was over and once the diameter of the cavity was too small to allow entry of the sponge.	• Complications during the procedure and until wound healing was complete • Recurrence rate in cases of cancer, • Mortality rate • Length of hospital stay, • Number of devices used in each patient • Number of days of treatment • Size of the cavity at onset of therapy • Number of days elapsing from surgery to the diagnosis of anastomotic dehiscence or rectal stump leakage, and those from diagnosis to the end of therapy	Of the 22 patients (m=18; f=4) with rectal cancer, 13 underwent anterior resection and colorectal anastomosis, and 9 underwent Hartmann's procedure. No complication was reported during procedure. In 2 patients (both from the anterior resection with ileostomy group), closure was not achieved, necessitating surgical intervention. 4 patients showed signs of recurrence after initially achieved successfully cavity closure. All 4 were retreated using the same protocol, and successful closure was achieved for 3 of them. 91% (20/22) (cavity closure) Full resolution was achieved without further surgery for a total of 19 patients, who were followed- up for a minimum period of 1 year. The mean time to achieve healing was 22.3 ± 14.7 days; 24.0 ± 15.5 days for the anterior resection group and 19.8 ± 14.09 days for the Hartmann group.	Small case series (high risk of bias). No comparator. Dates of procedure/data collection not provided. For 10 patients fibrin glue was used in addition after VAC therapy.

Milito (2017) Prospective non-comparative study, Italy (single centre)	Patients with anastomotic leakage following low anterior resection were candidates for the VAC therapy.	Intervention: EndoSPONGE. Mean anastomosis level was 5 cm (3-7). Patients received an intravenous antibiotic therapy with piperacillin+tazobactam (4.5g, 3 times/daily). Median time to leak diagnosis 14 days (range 7-21).	• Time to diagnosis of anastomotic leakage • Time of the outpatient therapy • Sponge exchanges for each patient • Healing time • Complications and side effects	14 patients were included in the study and underwent Endo-SPONGE. The diagnosis of anastomotic leakage was performed after a median interval of 14 days (range 7–21). Median healing time was 37 days (range 19–55). The median duration of the outpatient therapy was 35 days (range 16–51), with 3–14 sponge exchanges for each patient. 5 patients had mild anal pain.	Data in the table does not match information in the text (mean age) Small number of patients, observational study, single centre. .
Rottoli (2018) Prospective non-comparative study; Italy (single centre)	Patients who had a diagnosis of anastomotic leak after ileal pouch–anal anastomosis (IPAA). All leaks were symptomatic ad associated with signs of sepsis (March 2016 – March 2017).	Intervention: EndoSPONGE. The first application of the device was scheduled under deep sedation. Device was replaced every 48-72h.Antibiotic treatment was given at the time of diagnosis for at least 1 week and continues as long as necessary.	Primary outcomes: • The rate of successful healing at 6 months from the leak diagnosis Secondary outcomes: • Operative time – not discussed • Perioperative variables (time to anastomosis leakage diagnosis, time to • EndoSPONGE treatment and duration, hospital stay, ileostomy reversal, follow-up time, recurrence) • The rate of intra- and postoperative complications	72 patients underwent an IPAA procedure in the center. Among them, 8 patients were diagnosed with anastomotic leak and included in the study. The Endosponge treatment started at a median of 6.5 (1–15) days after diagnosis of the leakage and lasted for a median of 12 (3–32) days. The device was replaced a median of 3 (1–10) times. The median length of hospital stay after the first application of the treatment was 15.5 (6–48) days. All patients but one had their ileostomy reversed at a median of 2.5 (1–6) months from the endoscopic confirmation of healing.	Small case series, single centre. Lack of baseline characteristics. Outcomes (operative time) not discussed

Strangio (2015) Prospective non-comparative study; Italy (single centre)	Patients presenting with anastomotic leakage following colorectal surgery, with or without protective stoma (September 2008 and October 2013).	Intervention: EndoSPONGE. All patients received broad-spectrum antibiotics. In patients with protective stoma, parenteral nutrition was given when adequate oral food intake was not possible. In patients without a stoma, total parenteral nutrition was given with only clear fluids orally. At the first appearance of granulation tissue in the sinus cavity at endoscopy, oral diet was reintroduced.	• Complete healing of anastomotic leakage • Treatment failure requiring surgery • Closure of protective ileostomy and restoration of bowel continuity • Mortality • Number of sponges used • Time to leakage detection • Time to EndoSPONGE treatment	40 (13.4%) out of 296 patients were diagnosed with an anastomotic leakage following colorectal surgery. 25 were treated with EndoSPONGE. A complete healing of anastomotic leakage was achieved in 22 (88%) patients, whilst treatment failure occurred in the remaining 3 (12%) patients. Closure of protective ileostomy and restoration of bowel continuity was in 11 (84.6%) out of 13 patients. The median number of applications per patient was 9 (1–39 applications), for a duration of 4 weeks (range 1–32). The anastomotic leak was detected after a median of 17 days (range 0–102 days) after the surgical intervention. The endo-sponge treatment was applied after a median of 16 days (range 0–53 days) from anastomotic leakage detection.	No comparator. Small case series, single centre. Possible overlap with Manta (2016).
Arezzo (2015) Retrospective non-comparative study Italy (single centre)	Patients with a leak of a colorectal anastomosis who met the inclusion criteria were treated with endoscopic vacuum therapy. Inclusion criteria: all patients with acute or chronic leak in the presence of extraluminal abscess (November 2008 – June 2013) Exclusion criteria: presence of generalized peritonitis or	Intervention: Endo-SPONGE. Endo-SPONGE. Device replaced two or three times a week until complete healing of dehiscence was achieved. All chronic cases were treated as outpatient; acute were initiated on inpatient basis and discharged if the general conditions were	• Success rate (direct endo-scopic examination with the aid in all cases of direct water soluble contrast infection during endoscopy, showed a	14 (5 M, 9 F) patients were included. Median cavity length 4cm (2-9cm). Overall success rate was 79% (11/14): 89% (9/10) in acute leaks (<60 days) and 50% (2/4) in chronic leaks (>60 days) (P = 0.176). Among patients with diverting stoma, clinical success was 100% (8/8) while it was 50% (3/6) among patients without stoma (p= 0.055). 3 patients required further endoscopic treatment: an over the-scope-clip" was applied in two	Small case series, retrospective design, single centre. No comparator. Data in text and table don't match (sex distribution). One patient presented with recto-vaginal fistula

	haemodynamically unstable patient was a contraindication to endoscopic treatment. Minimum follow-up – 1 year.	favourable to proceed as outpatient.	complete restoration of the wall epithelium.) • Reasons for treatment failure • Time to complete healing • Number of sessions required (treatment sessions)	cases and fibrin-glue injection was performed in 1 case. The median duration of treatment was 12.5 sessions (range 4–40). The median time for complete healing was 40.5 days (range 8–114).	
Boschetti (2018) Retrospective non-comparative study France (2 centres)	People with clinical symptomatic anastomotic leakage. In most case, the leakage was diagnosed after a sepsis had been confirmed by a CT scan. A total of 29 patients included including 22 males and 7 females. At inclusion stage, 21 patients were referred for Endo-SPONGE treatment with a stoma systematically performed at the time of anastomosis (n=12) or secondly to treat sepsis (n=9). 23 with rectal cancer and 19 with neo-adjuvant chemoradiotherapy.	Intervention: Endo-SPONGE. Endo-SPONGE treatment was started in the month following surgery in 12 cases, and the mean delay was 35±56 weeks (8-260 weeks) in the remaining cases. These were cases referred from other centres due to failure of surgical or radiological treatments. Patients followed up endoscopically at 1, 3 and 6 months after treatment.	The outcomes are not defined in the methods of the study but the results report: • Time to closure • Number of sessions • Success rate • Reversal of protective stoma	Mean fistula length was 7cm±4.6cm (2-20cm). Mean distance from anal verge was 6.2cm±4.6cm (2-20cm). 12 patients were taking antibiotics when Endo-SPONGE was performed. Nutritional support was used in 3 patients The success rate was 93% (27/29) success (closure of cavity to <1cm). 24/29 successfully closed at 6 months. At 6 months, 85.7% (n=18) of patients presenting with a stoma had closure of stoma. Mean time to treatment to closure 10±6.5 (range 2-28) weeks. Mean number of treatment session was 18.6 ±13 (range 4-57). 1 patient with colon perforation following attempt to increase fistula size to facilitate endo-SPONGE treatment.	Retrospective Small sample size No comparator

Huisman (2019) Retrospective non-comparative study Netherlands (2 centres)	Patients with symptomatic AL after rectal surgery treated with Endosponge therapy. Inclusion/exclusion criteria: all eligible patients with symptomatic AL after rectal surgery treated with Endo-SPONGE therapy were included.	Intervention: Endo-SPONGE. Depending on surgeon preference, transanal closure of the defect was performed after a short period of Endosponge therapy (vacuum-assisted early transanal closure) to achieve shorter Endosponge therapy duration.	Primary outcome: restored gastrointestinal continuity at end of follow-up. Secondary outcomes: success rate; presence of a chronic sinus and the functional bowel outcome after AL (LARS score).	A total of 20 patients (M=14, F=6) were eligible for inclusion in our study. Median follow-up time: 10 months (range 3 to 84 months). Endosponge was successful in 17 of 20 patients (85%). In 14 of the 20 patients (70%), continuity was restored. Six patients received a definitive stoma. The median time from primary resection to stoma reversal was 10 [3–15] months.	The study intervention was Endo-Sponge followed by a planned surgical closure of defect. Small case series (high risk of bias). No comparator
Katz (2018) Retrospective non-comparative study Israel (single centre)	Patients with rectal anastomotic leaks were treated using the Endo-SPONGE system.	Intervention: Endo-SPONGE. In 5 patients, the endo-sponge was inserted manually, and in 1 patient, the endo-sponge was inserted via TAMIS approach after the failure of endoscopic insertion. No patient underwent irradiation prior to treatment	• Success rate • Restoration of bowel continuity • Number of sponge exchanges	A total of 6 patients (M=5; F=1). None of the patients underwent irradiation prior to surgery. Median dehiscence 180 (degrees) range 50-270 degrees Median time to leak diagnosis 7 days (range 4-14 days). Median time to first sponge placement 13 days (range 9-33). The mean number of Endo-SPONGE exchanges was 3.6 (range 3–5 exchanges). A diverting stoma was constructed in 2 out of 3 patients who had no previous diversion. All patients fully recovered and were discharged following completion of treatment. Four out of 5 patients with a diverting stoma underwent closure of their stoma following a computed tomography enema scan that confirmed an intact anastomosis.	Very small case series (high risk of bias). No comparator. Inclusion/exclusion criteria not reported. Discrepancy in reporting of stoma numbers between table and text of the study (table suggests 3/5 had a stoma already and 1/5 had a stoma created following leak diagnosis).
Keskin (2015) Retrospective non-comparative study Turkey (single centre)	Patients underwent Endo-SPONGE treatment for anastomotic	Intervention: Endo-SPONGE. The EndoSponge system was applied under midazolam sedation in the endoscopy	Success rate Cavity closure Results were also reported for lumen integrity, stoma	15 patients were included in this study. (M= 8, 55%; F=7,45%). Six patients had neoadjuvant treatment. An average of 15 (range, 6 to 27 d) days and 173 (range, 43 to 343 d)	Small case series (high risk of bias). No comparator.

	leakage separation identified during the early and late terms after proctectomy between May 2009 and May 2014.	unit. The sponge was changed every 3 to 4 days. Average number of sponge applications was 2.2 (range, 1 to 5). 12 patients treated as in-patients and 3 as out-patients.	closure rate, impact of early and late diagnosis on treatment success and any recurrent abscesses although these were not listed as outcomes in the methods	days elapsed between the surgery and anastomotic separation for the early-term and late-term cases. The average number of endosponge applications was 2.2 (range, 1 to 5). Eight leaks were identified early and 7 leaks identified late. In 12 (80%) patients, treatment was successful, and treatment in the remaining 3 patients (20%) was unsuccessful. In 2 patients, endosponge applications were discontinued due to progressing pelvic sepsis, and in 1 patient, endosponge application was discontinued due to bleeding inside the cavity. When early-term and late-term cases were evaluated separately, the success rates of endosponge treatment in terms of treatment completion and lumen integrity were 75% (6/8) and 85% (6/7) for early term and late-term cases respectively. In 10 of the 14 patients with stomas, the stomas were closed after endosponge application. Three patients (25%) were deceased due to systemic disease before stoma closure was achieved. The 2 former patients who developed enlarging cavities despite endosponge treatment underwent a second operation.	

Kuehn (2016) Retrospective non-comparative study Germany (single centre)	Patients with defects of lower gastrointestinal tract showing the signs of anastomotic leakage or rectal lesion. Considered for patients with signs of a localized peritonitis of the lower abdomen (September 2007 – February 2015).	Intervention: Endo-SPONGE. Placement was carried out in the surgical endoscopy unit, in the operating room or on the intensive care unit. Sponges were changed after 3 days. EVT usually performed without the need for sedation or anaesthesia	• Success • Closure of enterostomy and reasons for failure • Adverse events • Time to leakage detection • Therapy duration • Number of sponges used	41 patients over a time period of 8 years with a mean follow-up of 36 (2–89) months. The median number of sponge insertions was 6 (range, 1–37) with a mean changing interval of 3 days (range, 1–5). Median time of therapy was 20 days. A successful vacuum therapy with local control of the septic focus was achieved in 18 of 20 patients (90 %) with anastomotic leakage after rectal resection.	Small sample size, retrospective design, single centre. No comparator. No information regarding conflict of interests.
Manta 2016 Retrospective non-comparative study; Italy (2 centres)	Patients with a post-surgical leak involving the GI tract, irrespective of the previous surgical intervention type, who were referred to two Endoscopic Units to be treated with an endoscopic approach.	Intervention: The endoscopic treatments included: (1) OTSC positioning; (2) placement of a covered self-expanding metal stent (SEMS); (3) fibrin glue injection (Tissucol); and (4) endo-sponge application, according to both the endoscopic feature and the patient's status.	Fistula closure Length of stay was an outcome for the whole study cohort but not applicable to Endo-SPONGE as these were all outpatients.	Overall, 76 patients with a post-surgical leak involving the GI tract were treated with an endoscopic approach from April 2009 to September 2014. 7 were treated with Endo SPONGE. All treated were on an outpatient basis.2 also had radiological drainage. 100% (7/7) (complete leakage closure).	The study was not designed to investigate what method of closure was most effective therefore comparisons have not been made between the different treatment types. Baseline characteristics were not presented for Endo-SPONGE patients only. Small case series (high risk of bias), retrospective design. Possible overlap with Strangio (2015) as one study centre is the same

Mussetto (2017) Retrospective non-comparative study Italy (single centre)	Patients with anastomotic leakage treated with Endo-SPONGE were included in the study (March 2010 to February 2015). Every patient had a one-year colonoscopy as part of the oncological follow up and all underwent a clinical assessment every six months.	Intervention: Endo-SPONGE. Each patient had a follow-up colonoscopy and a contrast barium enema at least 2 months after complete closure of the abscess cavity. The therapy was performed under conscious sedation (meperidine (0.5-1mg/kg IV) and midazolam (2.5-5 mg IV)). The sponges were changed every 48-72 h. Closure was defined as a decreased cavity covered with granulation tissue that did not allow the insertion of a new sponge. Mean distance of anastomosis from anal verge was 4.5 cm (range 2-8). Mean size of leakage was 7.5 cm (range 4-12).	• Number of treatments • Number of days from treatment to closure • Closure of anastomotic leakage • Treatment failure • Relapse of leakage • Complications	11 patients (male: 6; mean age: 71 (range: 55-82) years were included. Ten out 11 patients (90.9%) showed closure of the anastomotic leakage after a mean of 16 (range: 9-23) sponge changes performed over a mean of 37 (range: 18-65) days. The ileostomy was subsequently closed in all the 10 patients with a closed abscess cavity. During follow up [mean 29 (range: 6-64) months], 2 cases of anastomotic stricture: 1 patient developed a stenosis 8 months after the removal of the Endo-SPONGE and was treated with endoscopic dilation; the other patient showed a stenosis after 5 months and was then successfully treated by placement of a fully covered stent that was removed after 5 weeks. Treatment failure was observed in 1 patient, who presented an increased size of dehiscence after 23 sessions of endoscopic treatment. 2 patients died during follow up from unrelated causes after 1 or 2 years follow-up.	Small number of patients, retrospective design, single centre. No comparator. Lack of exclusion criteria
Nerup (2013) Retrospective non-comparative study Denmark (2 centres)	Patients who underwent Low anterior resection (LAR) of the rectum in the period from 1st February 2008 to 1st February 2012. The inclusion criteria were as follows: patients with rectal cancer operated with LAR who developed an anastomotic leak and were	Intervention: Endo-SPONGE. The sponge was changes every second or third day. Treatment was ceased when the cavity was about 3 cm wide and covered in granulation tissue. Inpatient stay, some continued treatment as outpatient.	• Treatment success • Hospital stay • Number of treatments • Length of treatment • Mortality • Complications • Stoma closure rate	A total of 232 patients had undergone LAR for rectal cancer in the given four years period. 32 patients (14%) were identified as having had an AL. 15 (47%) of the patients with leaks were not re-operated and they were only treated with endoscopic vacuum therapy. 2 patients were excluded. All 13 patients treated with endoscopic vaccum achieved	Small number of patients, retrospective study design. Uneven sex distribution

	treated with endoscopic vacuum Therapy. The exclusion criteria were late onset endoscopic vacuum treatment more than one month after leakage diagnosis and patients who had not completed treatment at 1 February 2012. Patients with AL who required re-laparotomy were also excluded.			successful healing of the perianastomotic abscess cavity. The stoma closure rate of the entire study group was 12/13 (92%). The median length of hospital stay was 25 days (7-39 days). Some continued treatment in an outpatient setting. The median number of treatments per patient was 8 (1-18). The endoscopic vacuum treatment continued for a median of 18 days (3-40 days). None of the patients died during treatment. One patient developed a 10-cm long colon stenosis from the anastomotic site and proximally after an otherwise successful endoscopic vacuum treatment.	
Riss, Stift, Kienbacher (2010) Retrospective non-comparative study Austria (six centres)	Patients who had rectal cancer were undergone endo-sponge assisted treatment of anastomotic leakage (2006 to 2009). Sponge was changed at 2-3 days intervals. Median follow-up was 17 months (1.5 to 29.8)	Intervention: Endo-SPONGE.	• Follow-up duration • Time from primary operation to anastomotic leakage • Mortality • Complications • Stoma reversal • Duration of therapy	20 patients (M=13; F=7) were included in the study. 5 patients (25%) died (unrelated causes) during the follow-up period but were included in the analysis. The success rate was 75% (15 of 20 patients, including 10 did not have neoadjuvant treatment). At the time of endo-sponge treatment 9 patients (45%) had a diverting ileostomy and 8 patients (40%) a colostomy. In 13 patients (76.5%) the stoma was closed after successful endo-sponge treatment. The median duration of endo-sponge therapy was 21 days in both groups.	Long term follow up of patients successfully treated with Endo-SPONGE (follow-up of the patient group in Riss et al. 2010b). The EAC will only report the additional, unique outcomes from the long-term follow-up. Small number of patients. Lack of comparator Use of other non-operative interventions (fibrin glue, stent) Lack of conflicts of interest statement.

Riss, Stift, Meier (2009) Retrospective non-comparative study Austria (single centre)	Between 2007 and 2008, 9 patients who developed an abscess in the pelvis were chosen for endo-sponge. Hospitalization was only necessary for endo-sponge replacement or in case of poor general condition. During endo-sponge treatment, normal enteral alimentation was allowed to the patients.	Intervention: Endo-SPONGE. Antibiotics were administered in case of ongoing sepsis or peritonitis.	• Total time of treatment; • Duration of Endo-SPONGE replacement; • Complications • Treatment success • QoL: patient's satisfaction, alteration in daily life activity, pain sensation • Mortality	Nine patients (M=5; F=4) were included in the study. 4 (44.4%) of 6 patients in the LAR group had a stoma (one colostomy, three ileostomies) prior endo-sponge application. One patient showed an early anastomotic dehiscence 7 days after LAR. In all other patients (n = 8), the median time from primary surgery (LAR or Hartmann) to anastomotic leakage was 2.5 month (range: 1–24). The total time of endo-sponge treatment was a median of 3 weeks (range: 2–8). The median duration of each endo-sponge replacement was 15 min (range: 5–65). In 6 (66.6%) patients, the leakage healed successfully after treatment. Three patients showed no response and needed further surgical intervention. No minor or major complications observed during the endo-sponge treatment. One patient died during hospitalisation because of a heart attack after endo-sponge therapy.	Patients may overlap with Riss, Stift, Kienbacher (2010a) therefore the EAC will only report the long term outcoems from Riss et al (2010a) Small number of patients, retrospective study design, single centre. Lack of conflicts of interest statement. Some outcomes not presented separately for anastomotic leakage patients (n=9), rectal stump insufficiency n=3. Lack of detailed exclusion criteria.
Srinivasamurthy 2013 Retrospective non-comparative study UK (single centre)	All patients who underwent Endosponge treatment for anastomotic leakage between September 2007 and May 2011. Median time to leak detection 29 days (range 10-115)	Intervention: Endo-SPONGE. Each patient had only one Endosponge placed per application, except a single occasion of double sponge placement, and all were inserted under general anaesthetic.	• Complete closure or reduction in the abscess cavity size • Ileostomy reversal • Time to stoma reversal • Restoration of bowel continuity • Number of sponges used • Treatment period	Eight patients (M=7; F=1) had Endosponge therapy for extraperitoneal pelvic anastomotic leak during the 45-month study period. 6 had undergone pre-operative short course radiotherapy.The median number of sponge applications was 4 (range 1–7), over	Small sample size, single centre. Uneven sex distribution. Lack of comparator.

				a median treatment period of 26 days (range 7–49 days). Six out of 8 patients (75%) had complete closure or a reduction in the size of the abscess cavity. Five patients have had their ileostomies reversed over a median follow-up period of 41 months (range 10–45 months). Four out of five patients (80 %) who had Endosponge therapy instituted within 6 weeks of initial surgery have achieved restoration of bowel continuity with good results; only one of the three (33 %) who had treatment started after the 6 week watershed has achieved bowel continuity.	
van Koperen (2009 retrospective non-comparative study The Netherlands (multicentre)	Patients with a presacral cavity after anastomotic leakage (July 2006 – April 2008)	Intervention: Endo-SPONGE. The sponge is changed every 3 to 4 days. In 6 patients general anaethesia was used, and in 3 patients light sedation was used.	• closure of the cavity • The ability to close the ileostomy and factors associated with successful closure	N=16 (9 males, 7 females). Median age of 64 years (19-78).. Mean anastomosis level was 5 cm (2-8) from anal verge. 8/16 had stoma created during primary surgery. The median duration between the initial surgery and the discovery of the leakage was 11 days (range 3–150 days). Definitive resolution of the sinus was achieved in 9 out of 16 patients (56%). Closure was achieved in a median of 40 days (range 28 to 90 days) with a median of 13 sponge replacement (range 8 to 17). 5 of 9 patients with a closed abscess cavity the stoma had been closed. Bleeding in abscess cavity was seen in 1 patien. EndoSPONGE	Small number of patients, retrospective design. Lack of detailed inclusion and exclusion criteria Some centres had only 1 patient

				treatment was stopped in 1 patient after 13 exchange because the therapy was painful.	
Weidenhagen (2008): Retrospective non-comparative study Germany (single centre)	Patients with an anastomotic leakage after (low) anterior resection (2002-2004).	Intervention: Endo-SPONGE. Endoscopic vacuum device (describe Endo-SPONGE without mentioning the device name).	• Time of the diagnosis • The treatment duration • The number of sessions • Duration of hospital stay • Complications	N= 29 (24 male, 4 female). Mean age was 66.7 years (42-79). 9/29 received preoperative radio-chemotherapy. 5/29 had diabetes, 1/29 had a chronic intake of oral steroids. Protecting stoma created in 21/29 (19/21 protecting ileostomies, 2/21 colostomies) after primary surgery, 4/29 had stoma created after the secondary procedure. Definitive healing in 96.6% (28/29). Stoma was closed in 22/25. Time to closure was 168.9 ± 81.7 days (9-321 days). No major bleeding occurred, minor bleeding observed in some patients on removal of sponge. Mean hospital stay 30.5±12.8 (range 10-69	The conflict of interest between the authors and the company. Small number of patients, retrospective and observational study design, single centre. Imbalance in sex distribution. Lack of exclusion criteria.

4.2 Summary of economic evidence

The company and the EAC did not find any relevant economic studies.

De novo analysis

The company submitted a model which they described as a budget impact model comprising 2 separate decisions trees: Endo-SPONGE and the comparator percutaneous drainage. Each decision tree in the company model has 4 branches for different grades (1-4) of anastomotic leaks which leads to non-surgical treatment or surgical treatment. If the non-surgical treatment does not heal the anastomotic leak, the next step is surgical treatment. The final outcomes for all treatments are either a permanent stoma or a stoma reversed. The company developed its analytic model with a time horizon of 10 years with 1-year cycle and the EAC considered this was appropriate.

The company made a number of assumptions around the proportions of patients likely to be treated surgically or non-surgically and the proportions of patients whose anastomotic leak would not heal following non-operative treatment. Details of all assumptions that the company made in the model were described in Table 4 in the assessment report (page 78 to 79).

EAC revisions to the model

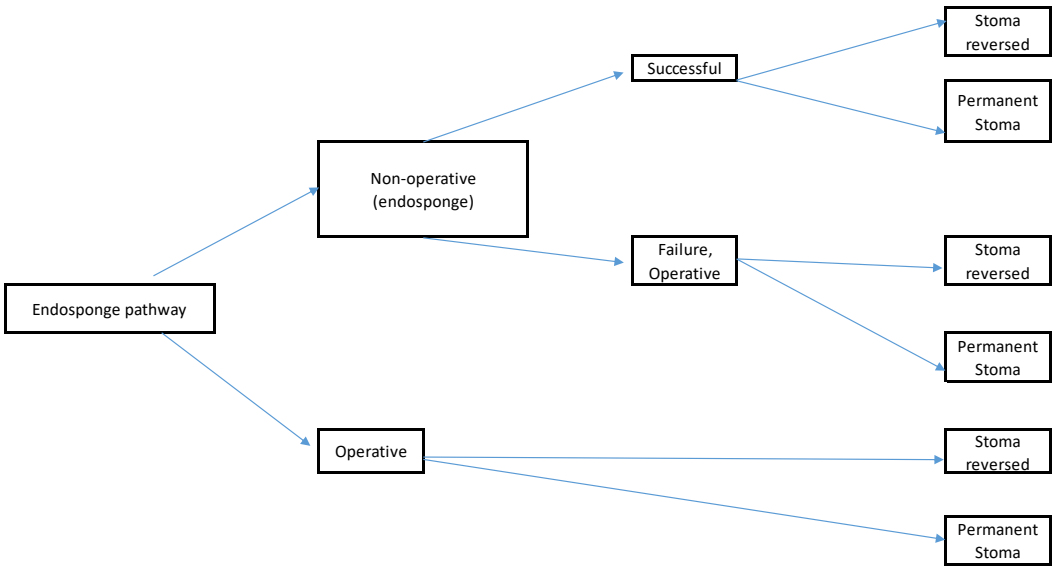
The EAC considered that the company's approach to the cost modelling using a budget impact model might be simply a difference in terminology and presentation. The company appeared to have used a budget impact template to create the model, and the results were presented for 100 patients rather than on an individual patient basis. The EAC used the structure of the company model as a starting point, revised the model and updated the parameters, presenting the results on a cost consequences basis.

The EAC was advised by clinical experts that the grading system is not widely used for clinical decisions when treating anastomotic leak so the EAC adjusted the decision trees to remove reference to the grade system. The EAC model is shown in Figure 1 (see below). The EAC noted that, on the basis of clinical evidence and expert advice, there is no standard treatment pathway for a patient diagnosed with anastomotic leakage. In clinical practice,

the use of antibiotic, sedation (general or local anaesthetic) or whether patients are treated in an inpatient or outpatient setting are likely to be driven by clinician or patient preference and are also dependent on the condition of the patient.

A similar decision tree was used for the comparator (Figure 1 and 2 in the assessment report, page 76 and 77).

Figure 1: EAC model for EndoSPONGE pathway decision tree.



The EAC proposed 3 possible scenarios based on the available evidence and expert advice and using a number of assumptions to calculate appropriate costs.

- Scenario 1 (EAC base case): Endo-SPONGE requires the first treatment to be inpatient with a general anaesthetic (GA) and theatre. Subsequent treatments are done in an outpatient setting (mild/no sedation)
- Scenario 2: Endo-SPONGE requires the first treatment to be inpatient with GA. Subsequent treatments are done as a theatre procedure on a day case basis (using GA).
- Scenario 3: EAC base-case with percutaneous drainage added. This scenario models the first treatment as an inpatient with a GA and theatre. A percutaneous drain was also placed at the same time. Subsequent treatments are done in an outpatient setting (mild/no sedation).

Details of all assumptions for each scenario were described in section 8.4 of the assessment report (page 81 to 83).

Model parameters

The main clinical parameters included in the company model included:

- the number of patients who are treated non-surgically either on the current pathway or with Endo-SPONGE
- the number of patients with a successful non-surgical outcome
- the number of patients who have subsequent surgical repair and
- the number of patients who have a stoma reversal following non-surgical and/or surgical treatment.

The EAC agreed that these are the key clinical parameters for consideration but have made some adjustments (details were reported in Table 5 of the assessment report, page 93):

- Proportion of patients treated non-surgically with Endo-SPONGE compared with current non-surgical treatment of leak. The EAC did not agree with the company assumption that Endo-SPONGE would result in an 25% increase of patients receiving non-surgical treatment compared with percutaneous drainage (67.7% vs 42.8%). The EAC assumed that the proportion of patients treated with either non-surgical treatment was the same (63%).The EAC noted that if the introduction of Endo-SPONGE does increase the proportion of patients routed to non-surgical treatment, there would be an increase in cost savings.
- Success rates for non-surgical treatment. The EAC base case assumed that 70% of percutaneous drainage treatments were successful based on the pooled success rate from 3 studies (the company used a success rate of 57.4% in the model).
- Proportion of patients who have a stoma reversal. The company assumed that 54.6% of patients receiving percutaneous drainage would have their stoma reversed following treatment compared with 71.2% of patients using Endo-SPONGE. The EAC base-case assumed that the rate of successful stoma reversal is 77.0% for Endo-SPONGE treatment and 62.0% for

percutaneous drainage treatment and 52.0% for stoma reversal following surgical treatment of anastomotic leaks.

Costs and resource use

The EAC noted that the company submission broke down the cost of treatment into the various component parts including staff costs, theatre costs, equipment costs etc., and most costs could be validated but some costs could not be validated; for example, stoma care costs. Details of costs used by the company and the EAC were described in section 8.5 of the assessment report (page 89 to 95).

Results

Base case results

The company submission estimated a cost saving of £2,419.5 per patient in year one with Endo-SPONGE. The cost saving in the company model was because treatment with Endo-SPONGE resulted in fewer patients needing re-operations more patients avoided a permanent stoma. In the company model, for every 100 patients treated the introduction of Endo-SPONGE would avoid 35 re-operations and 15 permanent stomas. In the EAC model with the revised parameters, this was reduced to 9 re-operations and 9 permanent stomas avoided per 100 patients.

The EAC base case results showed that Endo-SPONGE was cost incurring by £1,141.1 per patient in year 1 compared with percutaneous drainage. Over a 10 year time horizon, Endo-SPONGE was cost saving by £68.22per patient compared with percutaneous drainage. Table 2 presents the base case results.

Table 2: Comparison of company's and EAC's base case results over 1 year

	Company results			EAC results		
	Endo-SPONGE	Percutaneous Drainage	Cost saving per patient	Endo-SPONGE	Percutaneous Drainage	Cost saving per patient
Device	£2,916.8	£344.5	-£2,572.3	£3,227.1	£989.6	-£2,237.4
Reoperation	£5,022.9	£9,500.3	£4,477.3	£3,973.7	£4,776.7	£802.9
Permanent Stoma Cost (per year)	£899.5	£1,414.0	£514.5	£1,006.0	£1,299.4	£293.4
Total Costs	**£8,839.3**	**£11,258.8**	**£2,419.5**	**£8,206.8**	**£7,065.7**	**-£1,141.1**

Scenario analysis

The EAC also explored the other scenarios described above. For scenario 2 where Endo-SPONGE changes are done in a theatre procedure on a day case basis instead of in outpatients. The results showed that it would be cost incurring by £4,427.3 per patient compared with percutaneous drainage. In scenario 3 Endo-SPONGE would be cost incurring by £2,130.7 per patient because of the additional cost of patients receiving both percutaneous drainage and Endo-SPONGE (see Table 3 below).

Because there is no consensus on the clinical parameters, the EAC also ran the proposed scenarios with the clinical parameters values used in the company submission. Results showed that in scenario 1 Endo-SPONGE (Endo SPONGE changes were done as an outpatient basis) would save £724.4 per patient (1 year time horizon) and £2,829.3per patient (10 year time horizon) compared with percutaneous drainage.

In scenario 2 (Endo SPONGE changes were done as a day case), Endo SPONGE would be costing incurring by £2,792.1 per patient (1 year time horizon) and by £687.1 per patient (10 year time horizon).

The EAC concluded that the cost modelling suggests that conservatively Endo-SPONGE may not be cost saving in year 1 but savings would be realized over a 10 year time horizon. Although there is considerable uncertainty around the economic model inputs and subsequent cost savings, the impact of this uncertainty is minimised by the small number of patients likely to be treated.

Table 3: EAC's scenario analysis results

	1-year time horizon			10- years time horizon		
	Endo-SPONGE	Percutaneous Drainage	Cost saving per patient	Endo-SPONGE	Percutaneous Drainage	Cost saving per patient
EAC alternative parameters are applied to scenarios						
Scenario 1 (base case): 1st procedure with GA, subsequently in clinic	£8,206.8	£7,065.7	-£1,141.1	£12,353.4	£12,421.6	**£68.2**
Scenario 2: 1st procedure with GA, subsequently with GA as day case	£11,493.0	£7,065.7	-£4,427.3	£15,639.6	£12,421.6	-£3,218.0
Scenario 3: As Scenario 1, but all Endo-SPONGE patients also get Percutaneous Drainage	£9,196.4	£7,065.7	-£2,130.7	£13,343.0	£12,421.6	-£921.4
Company's clinical parameters are applied to scenarios						
Scenario 1 (base case): 1st procedure with GA, subsequently in clinic	£7,792.2	£8,518.1	**£724.4**	£11,517.1	£14,346.5	**£2,829.3**
Scenario 2: 1st procedure with GA, subsequently with GA as day case	£11,310.2	£8,518.1	-£2,792.1	£15,033.6	£14,346.5	-£687.1
Scenario 3: As Scenario 1, but all Endo-SPONGE patients also get Percutaneous Drainage	£8,852.72	£8,518.10	-£334.62	£12,576.09	£14,346.46	**£1,770.37**

5 Ongoing research

The company submission did not include details of any currently ongoing studies.

The EAC identified 1 observation study that is currently recruiting. This is an observational patient registry seeking to enrol 100 participants and is due to complete in 2025 (NCT02477930).

6 Issues for consideration by the Committee

Clinical evidence

The EAC considered Endo-SPONGE to be a safe and effective non-surgical way to manage anastomotic leaks but it highlighted the lack of the evidence comparing EndoSPONGE with other non-surgical interventions. Only 2 included studies (Schiffmann et al, 2019 and Wasmann et al, 2019) reported comparative outcomes. Schiffmann et al (2019) compared outcomes in patients treated with Endo-SPONGE who had previously been treated with neoadjuvant chemoradiotherapy with patients who had not been treated with chemoradiotherapy. Wasmann et al (2019) compared outcomes in patients who underwent Endo-SPONGE assisted early surgical closure with conventional management. The EAC noted that there is no definitive clinical pathway for treating anastomotic leaks and that the patient population is small, and this may explain the limited comparative evidence available on the use of Endo SPONGE.

The EAC considered the overall quality of the evidence was very low and there is a high risk of bias due to the retrospective design, limited - comparators and small study sample sizes. The EAC noted however that since the rate of anastomotic leaks from colorectal surgery in the UK is relatively low, the quality of the studies is unlikely to be improved . The EAC also mentioned that populations in the Endo-SPONGE studies were largely appropriate with cancer being the primary indication for colorectal surgery.

The clinical evidence suggests that the success rate in terms of achieving cavity closure for Endo-SPONGE treatment was 85% and the rate of stoma reversal after Endo-SPONGE treatment was 77%. However little evidence evaluated whether Endo-SPONGE is more effective in treating anastomotic leaks than the current standard non-surgical methods. The EAC also noted there is little quality of life evidence.

Clinical experts advised that there was no standard pathway for managing anastomotic leaks in the NHS and that treatment decisions were made on the basis of clinical assessment (i.e. severity of leakage) and patient condition. The EAC considered that a lack of standard treatment protocol may be a reflection of the fact that the number of patients diagnosed with anastomotic leak following colorectal surgery in the UK is very low. Clinical experts considered reduced time to stoma reversal and improvement in quality of life were the primary benefits from using Endo SPONGE.

Cost evidence

There is limited information available for many of the clinical parameters in the cost model. The cost modelling shows that in general the Endo-SPONGE device and procedure is more costly than the comparator, percutaneous drainage, but this cost may be offset by a reduction in the number of surgical re-operations, and permanent stomas. The evidence supporting the clinical parameters relating to the reductions in re-operations and permanent stomas is very uncertain and is likely to remain so given the small number of patients eligible for this treatment. The cost inputs also have a high degree of uncertainty because there is not a clearly defined clinical pathway, again in part due to the small numbers of patients seen in any treatment centre annually.

The main limitation of the economic modelling is a lack of consensus of for the care pathway for managing anastomotic leakage in the NHS. There was variation in the settings described in the literature and by clinical experts for Endo-SCOPE procedures. The EAC proposed 3 scenarios based on the available evidence using a number of assumptions to reflect the variation in current practice (Section 8.4 page 81) of the assessment report. Results from

the modelling shows that cost savings vary depending on the clinical parameters, time horizon and care pathway modelled.

7 Authors

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Bernice Dillon, Health technology assessment adviser

NICE Medical Technologies Evaluation Programme

March 2020

Appendix A: Sources of evidence considered in the preparation of the overview

A Details of assessment report:

Dr Susan O'Connell, Dr Helen Morgan, Edyta Ryczek, Megan Dale, Prof Grace Carolan-Rees. Cedar health technology research centre.

B Submissions from the following sponsors:

B Braun Medical Ltd.

C Related NICE guidance

No NICE guidance on anastomotic leakage.

D References

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Appendix B: Comments from professional bodies

Expert advice was sought from following experts who have been nominated or ratified by their Specialist Society, Royal College or Professional Body. The advice received is their individual opinion and does not represent the view of the society.

- Biju Aravind, consultant colorectal surgeon, East Kent Hospitals NHS Foundation Trust.
- Mark Cheetham, consultant surgeon and care group medical director, Shrewsbury and Telford NHS Hospital Trust
- Andrew Day, consultant general and colorectal surgeon, Surrey and Sussex Healthcare NHS Trust.
- Anandapuram Deepak Dwarakanath, consultant physician and medical director, North Tees and Hartlepool NHS Foundation Trust.
- Jim Khan, consultant colorectal & robotic surgeon, Portsmouth Hospitals NHS Trust.
- Edmund Leung, consultant colorectal surgeon, Hereford County Hospital.
- Ian Pearce, consultant urological surgeon and andrologist, Manchester University NHS Foundation.
- James Turvill, consultant gastroenterologist, York Teaching Hospital NHS Trust.

Please see the clinical expert statements included in the pack for full details.

Appendix C: decision problem from scope

	Draft scope issued by NICE
Population	People with an anastomotic leakage in the low colorectal area (extraperitoneal) after colorectal surgery.
Intervention	Endo-SPONGE
Comparator(s)	• Non-surgical interventions including antibiotics and/or percutaneous drainage • Surgical interventions (i.e. open drainage, laparoscopy with anastomotic repair, defunctioning stoma (i.e. loop ileostomy, loop transverse colostomy)) • It should be noted that the type of treatment a person receives is dependent on the severity of an anastomotic leakage.
Outcomes	The outcome measures to consider include: • the rate of anastomotic healing (i.e. closure of the cavity) • the percentage of cavity size reduction • time to heal • antibiotic usage (in defined daily doses) • the rate of re-operation, stoma formation and stoma reversal for anastomotic leakage • the rate of recurrent abscess formation • mortality rate • health related quality of life • length of hospital stay • length of intensive care stay • the rate of sepsis • the rate of complications (e.g. bleeding) • device-related adverse events.

Cost analysis	Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be long enough to reflect differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which will include scenarios in which different numbers and combinations of devices are needed.	
Subgroups to be considered	• The severity of anastomotic leakage (moderate versus severe) • Time to anastomotic leakage diagnosis and treatment (early versus delayed) • With versus without protective stoma Distance of anastomosis from anal verge	
Special considerations, including those related to equality	People having colorectal surgery will have an underlying condition such as inflammatory bowel disease or colorectal cancer. People who have been diagnosed with cancer and chronic diseases may be considered disabled under the Equality Act. Colorectal anastomotic leakage is more common in men; gender is a protected characteristic under the equality act.	
Special considerations specifically related to equality	Are there any people with a protected characteristic for whom this device has a particularly disadvantageous impact or for whom this device will have a disproportionate impact on daily living, compared with people without that protected characteristics?	No
	Are there any changes that need to be considered in the scope to eliminate unlawful discrimination and to promote equality?	No
	Is there anything specific that needs to be done now to ensure MTAC will have relevant information to consider equality issues when developing guidance?	No
Any other special considerations	Endo-Sponge may be particularly useful in people with significant co-morbidity because further surgery would be high risk for them..	

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology guidance scope

Endo-SPONGE for treating colorectal anastomotic leakage

1 Technology

1.1 Description of the technology

Endo-SPONGE (B. Braun) is a minimally invasive treatment for anastomotic leakage in the low colorectal area after colorectal surgery. The Endo-SPONGE system uses vacuum therapy, which is commonly used for the treatment of chronic and complex wounds.

The Endo-SPONGE system consists of an open pore sponge with a Redon drain, a sponge pusher, silicon overtube guides and a drainage set and system. It is designed to be used in conjunction with the Redyrob Trans Plus drainage bottle (B.Braun).

The sponge is inserted into the leakage cavity using a flexible endoscope or through open access via the anus. A drainage tube is connected to the sponge at one end and a drainage bottle at the other end. The bottle is a low-vacuum drainage container and exerts suction to provide continuous and constant negative pressure in the sponge. The system avoids the build-up of leaking discharge in the anastomotic leakage cavity and promotes the formation of granulation tissue and healing.

The size of the sponge in individual patients is cut according to the size of leakage cavity and up to 3 sponges may be placed into the cavity. The sponge is changed every 24 to 72 hours and is cut smaller with every application as the size of the cavity reduces. The number of sponges needed for completing treatment varies, ranging from 1 to 39. Sedation and analgesia may be needed for the insertion procedure. It may be necessary to use an

endoscopic dilation balloon to widen the entrance to the anastomotic cavity so that Endo-SPONGE can be inserted. Some potential risks associated with Endo-SPONGE are residual sponge particles, erosion of structures adjacent to sponge and injury to intestinal wall and bleeding.

The Endo-SPONGE system is not suitable when the following conditions are present: ileoanal or ileorectal cuff anastomotic leak, malignant tumour wound; necrotic tissue/gangrene; untreated osteomyelitis; anastomotic leakage directly adjacent to vessels; bladder or small bowels obstruction, non-drainable septic focus, systemic sepsis and clotting disorders.

1.2 Relevant diseases and conditions

The Endo-SPONGE system is intended for treating anastomotic leakage after colorectal surgery.

Anastomotic leakage refers to the escape of luminal bowel contents through a surgically created junction between two sections of bowel (McDermott et al., 2016). It is one of the most serious complications after colorectal surgery. Low anterior resections are associated with a leakage rate ranging from 1% to 24% (Kirchoff et al., 2010). Anastomotic leakage is associated with increased morbidity and mortality rates and can result in delayed wound healing, extended hospital stays and the need for a stoma (Clow et al., 2009, den Dulk et al., 2007). Anastomotic leakage also increases the need for reoperation, the risk of cancer recurrence and reduces both overall and disease free survival (Mirmezami et al., 2011).

In the UK, an analysis of the Hospital Episode Statistics database found that the rate of anastomotic leak following colorectal surgery was 6.4%, and anastomotic leakage was associated with higher rates of hospital mortality, 30-day readmission, and post-operative infection compared with no anastomotic leakage after colorectal surgeries (Wan et al., 2014). The study estimated that the hospitalisation associated with anastomotic leakage resulted in an additional cost of £2,651 and an extra length of stay of 9 days per patient compared with those without leakage after surgery.

Risk factors for anastomotic leakage can be broadly associated with patient and procedure related factors. Patient related factors include male gender, smoking, steroid use and nutritional status. Surgery related factors include longer operation time (i.e. longer than two hours), multiple blood transfusions, intraoperative contamination, and increased urgency of the operation (Khan et al., 2007). These risk factors are also noted in the guidance from the Association of Surgeons of Great Britain and Ireland on Prevention, Diagnosis and Management of Colorectal Anastomotic Leakage (March 2016) and are categorised as modifiable and non-modifiable risk factors as following:

- Modifiable risk factors:
  - Alcohol
  - Smoking
  - Obesity
  - Medication i.e. steroid, anti-TNF monoclonal anti-body, immunosuppressant, purine analogue immunosuppressant, VEGF inhibitor.
  - Nutrition and hypoalbuminaemia
  - Mechanical bowel preparation
  - Radiotherapy
  - Preoperative antibiotics and selective decontamination of the digestive tract
- Non-modifiable risk factors
  - Sex and age
  - History of radiotherapy
  - Diabetes
  - Emergency surgery
  - Tumour factors: distal anastomoses

1.3 Current management

Once a colorectal anastomotic leak has been diagnosed, the immediate principles in management relate to the treatment of potential contamination and resultant sepsis. Treatment choices available for anastomotic leakage

can be medical and conservative such as broad-spectrum antibiotics, parenteral nutrition, or nasogastric aspiration, with or without drainage of collected fluid and stoma formation. In addition, surgical approaches include, laparoscopy/laparotomy with anastomotic repair and de-functioning stoma, or abdominoperineal resection (Khan et al., 2008; Thomas and Margolin 2016).

NICE has not published guidelines on the treatment of colorectal anastomotic leakage. Guidance from the Association of Surgeons of Great Britain and Ireland on Prevention, Diagnosis and Management of Colorectal Anastomotic Leakage (March 2016) states that people with anastomotic leakage who are considered clinically stable may be treated conservatively using fluids, antibiotics and oxygen, with close clinical observation. However, for people showing signs of sepsis, steps must be taken to remove the source of the leak within 3 to 18 hours, depending on the underlying condition and severity of infection. In less severe cases of sepsis associated with extraperitoneal rectal anastomotic leakage, proximal defunctioning of the anastomosis with transanal or transperitoneal drainage may be considered. If there is radiological evidence that the anastomotic cavity is separate from the bowel, or if there are multiple sites of anastomotic leakage, surgical intervention is needed.

1.4 Regulatory status

Endo-SPONGE is a CE marked class (class IIb) medical device.

1.5 Claimed benefits

The benefits to patients claimed by the company are:

- Faster healing compared with conventional treatment
- Reduced risk of subsequent infection if the area is not infected
- Rapid control of the infection if the area is infected
- Reduced size of the anastomotic cavity
- Improvement in quality of life
- Reduced reoperation
- Reduced number of permanent stomas

The benefits to the healthcare system claimed by the company are:

- Reduced length of hospital stay after colorectal surgery
- Reduced healthcare utilisation through reversal of stomas
- Reduced resource use (i.e. fewer staff needed)
- Treatment in an outpatient clinic

2 Decision problem

Population	People with an anastomotic leakage in the low colorectal area (extraperitoneal) after colorectal surgery.
Intervention	Endo-SPONGE
Comparator(s)	• Non-surgical interventions including antibiotics and/or percutaneous drainage • Surgical interventions (i.e. open drainage, laparoscopy with anastomotic repair, defunctioning stoma (i.e. loop ileostomy, loop transverse colostomy)) It should be noted that the type of treatment a person receives is dependent on the severity of an anastomotic leakage.
Outcomes	The outcome measures to consider include: • the rate of anastomotic healing (i.e. closure of the cavity) • the percentage of cavity size reduction • time to heal • antibiotic usage (in defined daily doses) • the rate of re-operation, stoma formation and stoma reversal for anastomotic leakage • the rate of recurrent abscess formation • mortality rate • health related quality of life • length of hospital stay • length of intensive care stay • the rate of sepsis • the rate of complications (e.g. bleeding) • device-related adverse events.
Cost analysis	Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be long enough to reflect differences in costs and consequences between the technologies being compared.

	Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which will include scenarios in which different numbers and combinations of devices are needed.	
Subgroups to be considered	• The severity of anastomotic leakage (moderate versus severe) • Time to anastomotic leakage diagnosis and treatment (early versus delayed) • With versus without protective stoma • Distance of anastomosis from anal verge	
Special considerations, including those related to equality	People having colorectal surgery will have an underlying condition such as inflammatory bowel disease or colorectal cancer. People who have been diagnosed with cancer and chronic diseases may be considered disabled under the Equality Act. Colorectal anastomotic leakage is more common in men; gender is a protected characteristic under the equality act.	
Special considerations, specifically related to equality	Are there any people with a protected characteristic for whom this device has a particularly disadvantageous impact or for whom this device will have a disproportionate impact on daily living, compared with people without that protected characteristic?	No
	Are there any changes that need to be considered in the scope to eliminate unlawful discrimination and to promote equality?	No
	Is there anything specific that needs to be done now to ensure the Medical Technologies Advisory Committee will have relevant information to consider equality issues when developing guidance?	No
Any other special considerations	Endo-Sponge may be particularly useful in people with significant co-morbidity because further surgery would be high risk for them.	

3 Related NICE guidance

There is no related guidance for this technology.'

4 External organisations

4.1 Professional

The following organisations have been asked to comment on the draft scope:

- Association for Cancer Surgery
- Association of Laparoscopic Surgeons of Great Britain and Ireland
- Association of surgeon of Great Britain and Ireland

- Bladder and Bowel Foundation
- Royal College of surgeon
- The Association of coloprotology of Great Britain and Ireland

4.2 Patient

NICE's Public Involvement Programme identified the following organisations for patient commentary on the use of the technology during the guidance development:

- Beating Bowel Cancer
- Bowel Cancer UK
- Bladder and Bowel UK
- Colostomy UK
- Patient Liaison Group (ACPGBI)
- Pelican Cancer Foundation

NICE National Institute for Health and Care Excellence

Adoption report: MTG 461 Endo-SPONGE for treating colorectal anastomotic leakage

Summary

Adoption levers

- May reduce the number of permanent stomas and reoperations
- May improve patient experience and quality of life
- Provides an alternative to surgery for patients with an anastomotic leak
- May be cheaper than managing patients with a permanent stoma.

Adoption barriers

- Perceived poor quality of evidence to support its use from clinicians
- Poor patient tolerance of a tube protruding from anus for up to 6 weeks
- Lack of awareness of the technology by some clinicians
- Low usage due to infrequent need

1. Introduction

This adoption report includes some of the benefits and difficulties that may be faced by organisations when planning to adopt Endo-SPONGE into routine NHS use.

The technology described in this report is the Endo-SPONGE system which includes the Endo-SPONGE kit and Redyrob vacuum bottles.

2. Contributors

Adoption information was gathered from the company and 6 NHS staff. Three staff are based within the same NHS Trust. The table below provides more detail about the contributors and how Endo-SPONGE has been adopted in their trust.

Site	Job title	Experience
1	Consultant colorectal surgeon	Used in 8 to 10 patients in past 14 years (since the prototype was developed in 2005). 50-75% of patients have avoided permanent stoma.

Issue date: January 2020

2	Upper GI surgical specialty registrar	Used in 5 to 10 patients in past 2 years. 2 had an anastomotic leak following colorectal surgery, the others were upper GI patients.
2	Consultant colorectal surgeon	Used in 6 patients in the past 2 years. 5 were recalled, 2 for stoma reversal, 3 for further treatment.[1]
2	Consultant colorectal surgeon	Used in 2 patients and monitored another 2 patients in the past 18 months. 1 has had ileostomy reversed, 1 developed sepsis and had follow up colorectal surgery and 2 are still undergoing treatment.
3	Consultant physician and medical director – gastroenterologist and endoscopist	No experience with technology
4	Consultant colorectal surgeon	Used in 9 patients in past 8 years (across more than one trust). All 9 have avoided permanent stoma.

[1] User wants to note stoma reversal data in the table should not be used as outcome data for Endo-SPONGE. There may be other reasons why a stoma is not reversed despite having a healed anastomosis, such as functional issues or progressive disease.

3. Current practice in managing colorectal anastomotic leakage

Following colorectal surgery patients commonly have a temporary stoma to allow the lower bowel to heal. Contributors report their experience in using Endo-SPONGE has been with patients who have had or have ileostomies.

If the patient does not recover during the first week an anastomotic leak may be suspected. Investigations such as a contrast CT scan, gastrografin enema or flexible endoscopy may be carried out to confirm the diagnosis and extent of any leak.

Patients are then taken to emergency theatre to have a further investigation with flexible endoscopy (if not already carried out) and intervention with Endo-SPONGE under general anaesthetic.

One user estimated that of patients with an anastomotic leak approximately:

- half are suitable for Endo-SPONGE
- a quarter are managed conservatively, this may include a washout of the cavity, antibiotics and catheter tube to drain any fluid.
- a quarter have further surgery to remove the source of the leak commonly resulting in a permanent stoma.

4. Use of Endo-SPONGE in practice

Following a washout of the area, the Endo-SPONGE is cut to the size of the cavity prior to placement. The procedure takes 20 to 30 minutes.

Following the initial insertion of Endo-SPONGE users differ in their management of this technology. There are variations in frequency of changes to the technology and vacuum bottle (2-3 or 3-4 days). Four do this under sedation in an endoscopy suite which takes 15 minutes and 2 use general anaesthesia in theatre. Two users have changed Endo-SPONGE on outpatients in an endoscopy suite. The rationale for theatre use is access to the endoscopy suite and discomfort under sedation.

Two users have sent patients home with an Endo-SPONGE in place. They report issues in managing due to constraints in trust booking systems for non-urgent outpatient theatre slots and surgeon availability to change the technology 3 times per week. One patient disconnected the bottle at home and the vacuum stopped working delaying treatment. Other users are reluctant to send patients home with an Endo-SPONGE due to anxieties about the protruding tube.

All users agreed an average of 8 to 10 Endo-SPONGE insertions are required for treatment over 2 to 6 weeks. Other than one user who has placed 2 Endo-SPONGEs in one patient, all the other patients had treatment with 1 Endo-SPONGE at any time.

All users agreed that low levels of anastomotic leaks following colorectal surgery in the UK mean that the eligible patient population for Endo-SPONGE is small. Due to the small numbers of patients suitable for Endo-SPONGE, none of the users have developed a formal protocol for its use

The company report that 69 NHS trusts have used the technology across 77 hospitals in the UK between January 2018 to December 2019. The minimum order quantity is 1 pack of Endo-SPONGE (which includes 5 Endo-SPONGE kits) and 1 pack of 10 Redyrob bottles. There is a 5-year shelf life on the kits.

4. Reported benefits

The potential benefits of adopting Endo-SPONGE, as reported to the adoption team by the healthcare professionals using the technology or with expertise in this area are that it:

- May reduce the number of permanent stomas and reoperations
- May improve patient experience and quality of life by reducing the risk of a permanent stoma and preventing reoperation
- Provides an alternative to surgery for patients with an anastomotic leak
- May be cheaper than managing patients with a permanent stoma

5. Insights from the NHS

Patient selection

Endo-SPONGE is being used in patients with an anastomotic leak following colorectal surgery for a diagnosis of mid to low rectal cancer as indicated by the company. Users indicate it could be suitable for other indications such as an anastomotic leak with inflammatory bowel disease.

All users agreed that Endo-SPONGE is suitable for patients with a contained leak who are not significantly unwell. In cases of severe sepsis or deterioration after colorectal surgery, standard care would be to re-operate to resolve the underlying issue. One user expressed concern that if the technology is used in these highly unwell patients it could possibly delay an unavoidable re-operation with a risk of mortality or irreversible bowel damage.

The company state Endo-SPONGE can be used on a Hartmann's stump leak. One user expressed concerns using the technology for this indication because there is a risk that the small bowel could be injured if an abscess leak causes a fistula. Another user has used Endo-SPONGE successfully for this indication on 2 patients.

Two users agreed the technology is not suitable for chronic patients where an anastomotic leak has established, for example 4 to 6 weeks post-surgery. This is because in a later diagnosis the bowel tissue may have become fibrotic and the cavity where the leak has occurred would be difficult to shrink or collapse.

Clinician confidence and acceptance

All users considered the evidence available for the benefits of the technology to be of limited quality. There was no consensus on the real-world impact of the technology on reducing the number of permanent stomas, re-operations and control of infection by users. This is due to the small number of patients having treatment with Endo-SPONGE.

One user said because of the low number of patients suitable for the technology it is difficulty to develop expertise within a hospital. A national dataset was suggested which could be of benefit to users.

All agreed they wanted the option of using Endo-SPONGE for appropriate patients and all recognised the benefits of vacuum therapy for anastomotic leaks.

One user suggested that whilst the technology has been available and used by early adopters since 2005 there is poor awareness in the colorectal surgical community. Adoption would be supported by inclusion in the Association of Surgeons of Great Britain and Ireland, prevention, diagnosis and management of colorectal anastomotic leakage algorithm.

Resource impact and Procurement

All users agreed Endo-SPONGE would be cost saving if it prevents a permanent stoma and reduces the need for managing a progressive anastomotic leak. No users had any data to support this.

All users order the technology alongside other surgical equipment and have not had to seek financial permission by the trust or commissioners.

Users described the Endo-SPONGE pack of 5 kits and Redyrob 10 bottle packs as bulky and costly if it is not being used straight away and is stored in theatre awaiting a suitable patient. A starter pack of 1 Endo-SPONGE kit 1 Redyrob vacuum bottle would be a useful addition to users.

Training

Consultant surgeons or senior registrars with endoscopy experience are currently placing Endo-SPONGE. A consultant surgeon is often required to be on call due to the complexity of managing this patient group. Most users agreed it is easy to place Endo-SPONGE if they have experience in this area (medical endoscopist or gastroenterologist).

Training is available from the company but the low numbers and need for the procedure to be done as an emergency meant some users observed and learnt from colleagues. One user suggested simulator training would be beneficial.

The company offer a presentation and product overview, included a non-clinical demonstration of how the treatment works. The aim is to deliver direct or a train the

trainer teaching model to surgeons and nurses who may eventually be involved in managing Endo-SPONGE patients in due course.

Complications

As the tube is stiff due to vacuum therapy, one user suggested a risk of anal and bowel tissue erosion is possible, no users reported this.

One user raised a concern about patients having a general anaesthetic 3 times a week for up to 6 weeks. No users reported any incidents.

Patient acceptance

Most users agreed patient acceptance was initially good in that they were happy to use Endo-SPONGE, when they were aware of benefits, such as avoiding re-operation and reducing the risk of a permanent stoma. But 1 user had to abandon the treatment with 3 patients due to discomfort from the protruding tube. Another user struggles to get any meaningful feedback from patients about the technology due to them being in the middle of a life-threatening complication following a cancer diagnosis.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technologies guidance

MT461 – Endo-SPONGE for colorectal anastomotic leakages

Company evidence submission

Part 1: Decision problem and clinical evidence

Company name	B Braun Medical Ltd
Submission date	6th January 2020
Regulatory documents attached	CE certificate, Declaration of Conformity, instructions for use, Environmental certificates (x2)
Contains confidential information	No

Contents

1 Decision problem

	Scope issued by NICE	Variation from scope (if applicable)	Rationale for variation
Population	People with anastomotic leakage in the low colorectal area (extra peritoneal) after colorectal surgery	N/A	N/A
Intervention	Endo-SPONGE	N/A	N/A
Comparator(s)	Non-surgical interventions including antibiotics and/or percutaneous drainage Surgical interventions (i.e. open drainage, laparoscopy with anastomotic repair, defunctioning stoma (i.e. loop ileostomy, loop transverse colostomy)) It should be noted that the type of treatment a person receives is dependent on the severity of an anastomotic leakage	N/A	N/A
Outcomes	The rate of anastomotic healing (i.e. closure of the cavity) The percentage of cavity size reduction Time to heal Antibiotics usage (in define daily doses) The rate of re-operation, stoma formation and stoma reversal for anastomotic leakage The rate of recurrent abscess formation Mortality rate Health related quality of life Length of hospital stay Length of intensive care stay The rate of sepsis The rate of complications (e.g. bleeding) Device related adverse events	N/A	N/A
Cost analysis	Costs will be considered from and NHS and personal social services perspective. The time horizon will be long enough to reflect differences in costs and consequences between the technologies being compared.	Enter text.	Enter text.

	Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which will include scenarios in which different numbers and combinations are needed.		
Subgroups to be considered	The severity of anastomotic leakage (moderate versus severe) Time to anastomotic leakage diagnosis and treatment (early versus delayed) With versus without protective stoma Distance from anal verge	Enter text.	Enter text.
Special considerations, including issues related to equality	People having colorectal surgery will have underlying condition such as inflammatory bowel disease or colorectal cancer. People who have been diagnosed with cancer and chronic diseases may be considered disables under the Equality Act. Colorectal anastomotic leakage is more common in men; gender is a protected characteristic under the equality act.	Enter text.	Enter text.

2 The technology

Give the brand name, approved name and details of any different versions of the same device (including future versions in development and due to launch). Please also provide links to (or send copies of) the instructions for use for each version of the device.

Brand name	Endo-SPONGE
Approved name	Endo-SPONGE
CE mark class and date of authorisation	Class IIa medical device 29.04.2019

Version(s)	Launched	Features

5526510	2009	Pack of 10 kits
		• Endo-SPONGE®, open-pore PUR sponge (ø 3.3 x 7.5 cm) with Redon drain CH12, med. PVC, 40 cm long
		• Pusher, ABS + PVC, CH 30, 30 cm long
		• Overtubes in 2 sizes, depending on device and sponge size
		  ○ Silicon tube, each 29 cm long
		  ○ Tapered rounded tip
		  ○ Size 1: inner diameter 13 mm, outer diameter 17 mm
		  ○ Size 2: inner diameter 15 mm, outer diameter 19 mm
		• Irrigation set comprised of 20 ml syringe + cap + slide clamp
		• Y connecting tube with Luer lock fitting

5526520	2009	Pack of 5 kits
		• Endo-SPONGE®, open-pore PUR sponge (ø 3.3 x 7.5 cm) with Redon drain CH12, med. PVC, 40 cm long
		• Pusher, ABS + PVC, CH 30, 30 cm long
		• Overtubes in 2 sizes, depending on device and sponge size
		  ○ Silicon tube, each 29 cm long
		  ○ Tapered rounded tip
		  ○ Size 1: inner diameter 13 mm, outer diameter 17 mm
		  ○ Size 2: inner diameter 15 mm, outer diameter 19 mm
		• Irrigation set comprised of 20 ml syringe + cap + slide clamp
		• Y connecting tube with Luer lock fitting

5526604	2002	Redyrob® Trans Plus – controllable wound drainage system. Pack of 10 bottles
Enter text.	Enter text.	Enter text.
Enter text.	Enter text.	Enter text.

What are the claimed benefits of using the technology for patients and the NHS?

Claimed benefit	Supporting evidence	Rationale
Patient benefits		
High success rate (anastomotic healing rate)	Arezzo et al 2015, Boschetti et al 2018, Huisman et al 2019, Jimenez-Rodriguez et al 2018, Katz et al 2018, Keskin et al 2015, Manta et al 2016, Mussettos et al 2017, Nerup et al 2013, Riss et al 2010, Riss et al 2009, Rottoli et al 2018, Srisvanmurthy et al 2013, Strangio et al 2015, Van Koperan et al 2009, Weidenhagen et al 2008 Systematic reviews: Shalaby et al 2019 and Popivanov et al 2019	Meta-analysis submitted here (section 7) demonstrates weighted mean 88.8% success rate of AL healing following Endo-SPONGE treatment. Two separate systematic reviews with meta-analysis report weighted mean success of 85.4 and 85.3% success rate
High stoma reversal rate – fewer permanent stoma, impact on patients' quality of life	Boschetti et al 2018, Huisman et al 2019, Jimenez-Rodriguez et al 2018, Katz et al 2018, Keskin et al 2015, Kuehn et al 2016, , Nerup et al 2013, Riss et al 2010, Rottoli et al 2018, Srisvanmurthy et al 2013, Strangio et al 2015, Van Koperan et al 2009, Weidenhagen et al 2008 Systematic reviews: Shalaby et al 2019 and Popivanov et al 2019	Meta-analysis submitted here (section 7) demonstrates weighted mean 79.0% stoma reversal following Endo-SPONGE treatment. Two separate systematic reviews with meta-analysis report weighted mean stoma reversal of 84.5 and 72.6% success rate
High bowel continuity – High patient quality of life	Huisman et al 2019, Jimenez-Rodriguez et al 2018, Katz et al 2018, Keskin et al 2015 and Srisvanmurthy et al 2013,	Meta-analysis submitted here (section 7) demonstrates weighted mean 72.1% successful bowel continuity following Endo-SPONGE treatment.
High long term success – fewer relapses of AL,	Boschetti et al 2018, Jimenez-Rodriguez et al 2018, Mussettos et al 2017, Riss et al 2009, Rottoli et al 2018	Meta-analysis submitted here (section 7) demonstrates weighted mean 84.8% long term success following Endo-SPONGE treatment.
Low complication rate – fewer extra interventions	Arezzo et al 2015, Boschetti et al 2018, Huisman et al 2019, Jimenez-Rodriguez et al 2018, Keskin et al 2015, Kuehn et al 2016, Milito et al 2016, Nerup et al 2013, Riss et al 2010, Riss et al 2009, Srisvanmurthy et al 2013, Strangio et al 2015, Van Koperan et al 2009, Weidenhagen et al 2008 Systematic review: Shalaby et al 2019	Meta-analysis submitted here (section 7) demonstrates weighted mean 10.0% complication rate following Endo-SPONGE treatment. A separate systematic review with meta-analysis reports 11.1% complication rate

Low need for extra surgery – reduce risk to patient	Arezzo et al 2015, Boschetti et al 2018, Huisman et al 2019, Jimenez-Rodriguez et al 2018, Katz et al 2018, Keskin et al 2015, Manta et al 2016, Mussettos et al 2017, Nerup et al 2013, Riss et al 2010, Riss et al 2009, Rottoli et al 2018, Srisvanmurthy et al 2013, Strangio et al 2015, Van Koperan et al 2009, Weidenhagen et al 2008	Meta-analysis submitted here (section 7) demonstrates weighted mean 11.0% requirement for extra surgery following Endo-SPONGE treatment.
Short duration of stoma – improved quality of life to patient and reduced risk of potential stoma related complications	Huisman et al 2019, Kuehn et al 2016, Rottoli et al 2018, Srisvanmurthy et al 2013 and Weidenhagen et al 2008	Meta-analysis submitted here (section 7) demonstrates time to stoma reversal of 10.4 months
System benefits		
High long term success – fewer relapses of AL, reduced re-admittance and risk to patients	Boschetti et al 2018, Jimenez-Rodriguez et al 2018, Mussettos et al 2017, Riss et al 2009, Rottoli et al 2018	Meta-analysis submitted here (section 7) demonstrates weighted mean 84.8% long term success rate following Endo-SPONGE treatment.
Outpatient treatment – reducing length of stay and pressures on beds	Arezzo et al 2015, Boschetti et al 2018, Jimenez-Rodriguez et al 2018, Keskin et al 2015, Manta et al 2016, Milito et al 2016 Rottoli et al 2018 and Weidenhagen et al 2008	103/130 (79%) (weighted mean 79.8%) patients were treated as outpatients in these studies.
Reduced need for extra surgery – reduce resource requirement, and LOS	Arezzo et al 2015, Boschetti et al 2018, Huisman et al 2019, Jimenez-Rodriguez et al 2018, Katz et al 2018, Keskin et al 2015, Manta et al 2016, Mussettos et al 2017, Nerup et al 2013, Riss et al 2010, Riss et al 2009, Rottoli et al 2018, Srisvanmurthy et al 2013, Strangio et al 2015, Van Koperan et al 2009, Weidenhagen et al 2008	Meta-analysis submitted here (section 7) demonstrates weighted mean 11.0% requirement for extra surgery following Endo-SPONGE treatment.
Low requirement for antibiotics	Boschetti et al 2018, Huisman et al 2019, Jimenez-Rodriguez et al 2018, Katz et al 2018 and , Van Koperan et al 2009	17/112 patients used antibiotics before or with Endo-SPONGE from 5 papers. All other papers did not mention antibiotic use. Weighted mean 10.9 % antibiotic use

Cost benefits		
High stoma reversal rate – reduction in on going stoma care, with fewer patients resulting in and end stoma	Boschetti et al 2018, Huisman et al 2019, Jimenez-Rodriguez et al 2018, Katz et al 2018, Keskin et al 2015, Kuehn et al 2016, , Nerup et al 2013, Riss et al 2010, Rottoli et al 2018, Srisvanmurthy et al 2013, Strangio et al 2015, Van Koperan et al 2009, Weidenhagen 2008 Systematic reviews: Shalaby et al 2019 and Popivanov et al 2019	Meta-analysis submitted here (section 7) demonstrates weighted mean 79.0% stoma reversal rate following Endo-SPONGE treatment. Two separate systematic reviews with meta-analysis report weighted mean stoma reversal of 84.5 and 75.9%.
High long term success – fewer relapses of AL, reduced re admittance and risk to patients	Boschetti et al 2018, Jimenez-Rodriguez et al 2018, Mussettos et al 2017, Riss et al 2009, Rottoli et al 2018	Meta-analysis submitted here (section 7) demonstrates weighted mean 84.8% long term success following Endo-SPONGE treatment.
Outpatient treatment – reducing length of stay and pressures on beds	Arezzo et al 2015, Boschetti et al 2018, Jimenez-Rodriguez et al 2018, Keskin et al 2015, Manta et al 2016, Rottoli et al 2018 and Weidenhagen et al 2008	89/124 patients were treated as outpatients in these studies reducing need for hospital stay
Reduced need for extra surgery – reduce resource requirement, and LOS	Arezzo et al 2015, Boschetti et al 2018, Huisman et al 2019, Jimenez-Rodriguez et al 2018, Katz et al 2018, Keskin et al 2015, Manta et al 2016, Mussettos et al 2017, Nerup et al 2013, Riss et al 2010, Riss et al 2009, Rottoli et al 2018, Srisvanmurthy et al 2013, Strangio et al 2015, Van Koperan et al 2009, Weidenhagen et al 2008	Meta-analysis submitted here (section 7) demonstrates weighted mean 11.0% requirement for extra surgery following Endo-SPONGE treatment.
Reduced duration of stoma – reduced stoma consumables costs and risk of complications	Huisman et al 2019, Kuehn et al 2016, Rottoli et al 2018, Srisvanmurthy et al 2013 and Weidenhagen et al 2008	Meta-analysis submitted here (section 7) demonstrates time to stoma reversal of 10.4 months
Reduced costs compared with conventional treatment	Arezzo et al 2015	Endo-SPONGE treatment cheaper than surgical approach and fewer patients will need surgery following Endo-SPONGE treatment

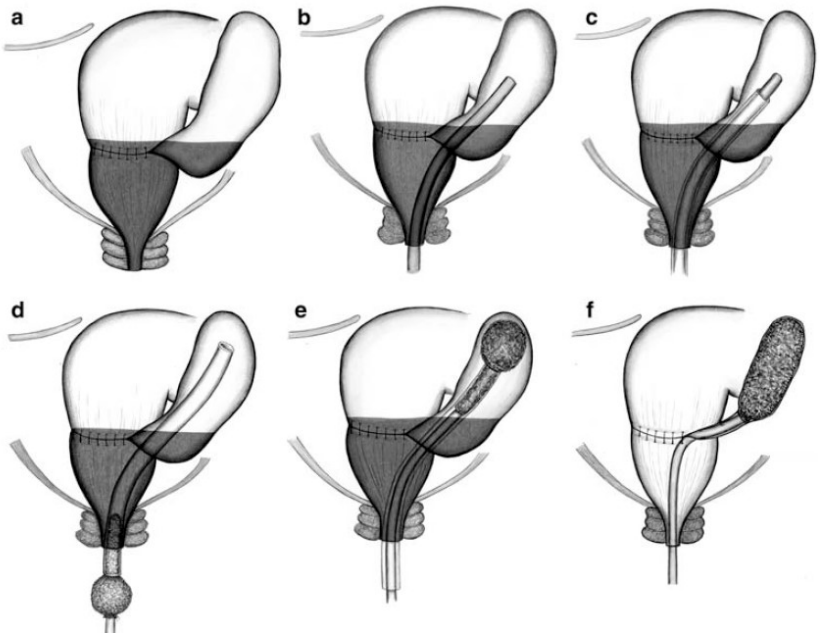
Sustainability benefits		
High stoma reversal rate – reduction in on going stoma care, with fewer patients resulting in and end stoma, fewer stoma consumables to be disposed of	Boschetti et al 2018, Huisman et al 2019, Jimenez-Rodriguez et al 2018, Katz et al 2018, Keskin et al 2015, Kuehn et al 2016, , Nerup et al 2013, Riss et al 2010, Rottoli et al 2018, Srisvanmurthy et al 2013, Strangio et al 2015, Van Koperan et al 2009, Weidenhagen 2008 Systematic reviews: Shalaby et al 2019 and Popivanov et al 2019	Meta-analysis submitted here (section 7) demonstrates weighted mean 79.0% stoma reversal following Endo-SPONGE treatment. Two separate systematic reviews with meta-analysis report weighted mean stoma reversal of 84.5 and 75.9% success rate
Reduced duration of stoma – reduced stoma consumables for disposal	Huisman et al 2019, Kuehn et al 2016, Rottoli et al 2018, Srisvanmurthy et al 2013 and Weidenhagen et al 2008	Meta-analysis submitted here (section 7) demonstrates time to stoma reversal of 10.4 months

Briefly describe the technology (no more than 1,000 words). Include details on how the technology works, any innovative features, and if the technology must be used alongside another treatment or technology.

Endo-SPONGE consists of an open-pored sponge connected to a drainage tube. After endoscopic insertion of the sponge into the leakage cavity the drainage tube is routed out through the anus and connected to a vacuum system. The application of the vacuum leads to a continuous drainage of the fluid and the sponge in the cavity promotes the cleaning of the surface. To achieve an effective treatment the size of the sponge is cut to fit the cavity. Depending on the size of the leakage cavity it can be necessary to place more than one sponge into the cavity. The sponge system is changed every 48–72 hours. To change the sponge the vacuum is disconnected. Removal of the sponge is easier with prior irrigation with 0.9 % saline solution to remove the granulated tissue from the surface of the sponge. The sponge is removed through the anus and size of the new sponge is adapted to the size of the leakage cavity.

Once granulation tissue has started to form in the cavity the new sponge should be cut down to the appropriate size before insertion, this mechanically forces the cavity to reduce in size. The sponge can be cut along the width and length and the tube in the sponge can be cut through as well.

Endo-SPONGE treatment is stopped when the cavity reaches a size of 2 x 1 cm, because no further reduction of the sponge size is technically possible



Vacuum-assisted wound closure process (Weidenhagen et al. 2008c)

The Endo-SPONGE® kit contains an Endo-SPONGE®, overtube in 2 different sizes (to accommodate different sized endoscopes), pusher, irrigation set (syringe and tip), and clamp, Y-connector and connecting tube with luer lock attachment to Redyrob® bottle. Not contained in the kit but required for the treatment are the Redyrob® bottle and hydro gel. The treatment is placed endoscopically via the anus under mild sedation if required. Depending on the cavity size, multiple endo-SPONGES (up to a maximum of 3) can be placed within the cavity.

Briefly describe the environmental impact of the technology and any sustainability considerations (no more than 1,000 words).

Responsible treatment of the environment

B Braun Medical is an example of sustainable development and has obtained environmental certification according to ISO 14001:2015. It is registered in the EMAS (Eco-Management Audit Scheme, Regulation (EC) No. 1505/2017) of environmental excellence, having passed the audit for companies B. Braun Medical, S.A., B. Braun Surgical, S.A., B. Braun VetCare, S.A. and B. Braun Logistics, S.L.

In accordance with the ethical values of our cultural environment, in the development of which B. Braun wishes to participate, we maintain a responsible treatment with the environment, applying practices that favour its protection, keeping our emissions under control and influencing the rationalisation of the use of natural resources and helping the conservation of the surrounding environment, following the basic principles of a circular economy and always working from the perspective of the life cycle, both in the manufacture of our products and in the prioritisation in the acquisition of materials, products and the contracting of services that respect the environment.

To this end, we have adopted the following commitments:
- We apply a policy of respect for the environment, reducing emissions and the consumption of natural resources, prioritising those aspects that have been identified as significant, such as water and energy.
- We manage waste following the criterion of a "circular economy" and adopting the perspective of the life cycle of the product.
- We encourage our suppliers to adopt environmental standards, prioritising the acquisition of materials and products that are respectful of the environment and ensuring compliance with the requirements of the Environmental Management System (EMS) by external suppliers operating in our facilities.
- We provide our customers with environmental information about our products and collaborate with the Administration in order to promote environmental improvements.
- We are proactive in communication, for which we have an environmental communication plan and, as a culmination of this strategy, we have B. Braun's environmental declaration, which we update annually and which we make available to all interested parties through our intranet and our website.

Specifically with regards Endo-SPONGE, the packaging was recently updated to reduce waste and it now has a 5 year shelf life. This is beneficial because if you have some spare after a patients treatment has finished, it will remain useable for a while after so will not need to go to waste. The packaging and product should all be disposed of by the medical team in the proper manner for medical devices, none of it is currently recyclable.

With the quicker stoma reversal time compared to the current pathway, as well as a higher rate of stoma reversals there would be a less patients who require stoma products and consumables on an ongoing basis. There would also be less waste produced by these products that would need to be disposed of.

3 Clinical context

Describe the clinical care pathway(s) that includes the proposed use of the technology, ideally using a diagram or flowchart. Provide source(s) for any relevant pathways

The aim of the treatment of AL must be to address the consequences of the leakage, which may lead to ongoing infection and development of severe septic states. Treatment to achieve this includes treatment of the infection, cleaning of the cavity, healing promotion and sealing of the defect. Since the nature of the leaks from the Hartmann's stump and from the anastomotic procedures are similar in nature, alignment is considered in terms of management. However, the scientific focus of discussion seems to lean towards anastomotic leakages throughout the medical publications.

There is no universally accepted management flowchart for anastomotic leakage (Shalaby et al. 2019). Treatment should be individualized based on the patient's general condition, anastomotic defect size and location, indication for primary resection and the presence of a proximal stoma. However, there has been a paradigm shift in the management of anastomotic leakage from surgical to non-operative image-guided and, more recently, endoscopic treatment (Daams, Luyer, and Lange 2013).

Guidance on prevention, diagnosis and management of colorectal anastomotic leakage from the Association of Surgeons of Great Britain and Ireland (F D McDermott et al. 2016) states that people with anastomotic leakage who are considered clinically stable may be treated conservatively using fluids, antibiotics and oxygen, with close clinical observation.

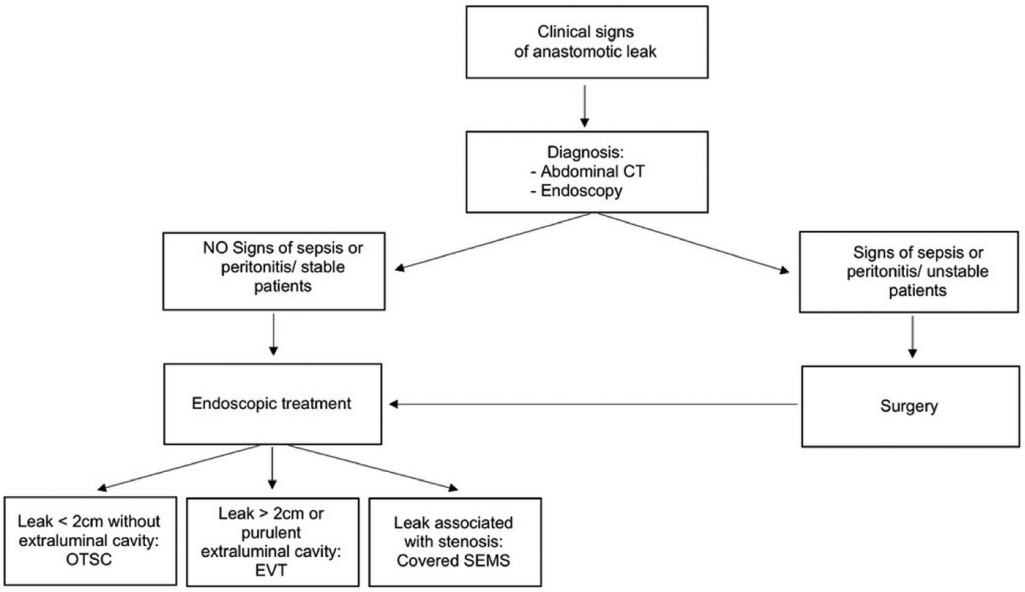
However, for people showing signs of sepsis, steps must be taken to remove the source of the leak within 3 to 18 hours, depending on the underlying condition and severity of infection. In less severe cases of sepsis associated with extra peritoneal rectal anastomotic leakage, proximal defunctioning of the anastomosis with transanal or trans peritoneal drainage may be considered. If there is radiological evidence that the anastomotic cavity is separate from the bowel, or if there are multiple sites of anastomotic leakage, surgical intervention is needed.

Conservative treatment requires a thorough assessment of the patient's clinical stability. A stable patient may initially be adequately managed conservatively, with intestinal rest, antibiotics and oxygen, together with close clinical observation.

Non-Surgical Intervention

Antibiotics are often the first line of treatment in a symptomatic but stable patient and may be used alone or in combination with percutaneous drainage or reoperation depending on the severity of the leak. Treatment with broad-spectrum antibiotic with gram negative and anaerobic coverage is a reasonable option for small fluid collections that are not amenable to percutaneous drainage (Thomas and Margolin 2016).

Treatment decision tree (Verra et al. 2019)



OTSC: Over The Scope Clip; EVT: Endoscopic Vacuum Therapy; SEMS: Self-Expandable Metal Stents

Image-guided percutaneous drainage has become an attractive alternative to reoperation because of decreased morbidity and hospital stay (Byrne et al. 2016).

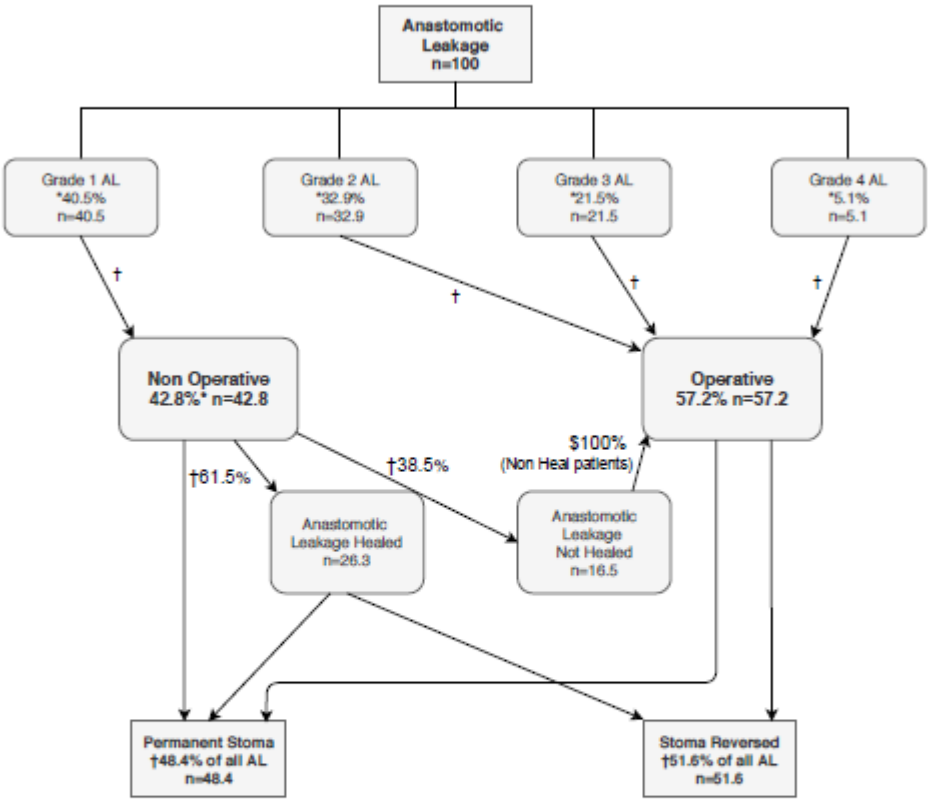
During an examination under anesthesia, proctoscopy can be used to place a drain through the defect into the extra luminal fluid collection. This is especially effective in cases of small (<1 cm) defects with a draining sinus cavity in the pelvis. Placement of a transanal drain also allows for follow-up radiographic surveillance of the abscess cavity by the instillation of contrast through the drain. The drain may be removed when the cavity has decreased to the size of the drain. Successful resolution of the defect does not remove the risk of long-term complications associated with anastomotic leaks such as stricture formation and poor bowel function. Continuing leakage of enteric contents or lack of clinical improvement should be treated with more aggressive interventions (Thomas and Margolin 2016).

Emerging newer, non-surgical procedures, include stents, self-expanding stents, endoscopic clips and tissue sealants.

Surgical Intervention

Development or deterioration in the severity of sepsis in a patient treated conservatively or by radiological drainage for AL should be considered “failed” treatment and a low threshold maintained for taking a patient urgently to theatre and taking down the anastomosis (F D McDermott et al. 2016). Source control with washout and fecal diversion are the main goals of surgical intervention for anastomotic leak. Second surgeries come with all surgical risk and associated impact on length of stay for the patient.

Current Process



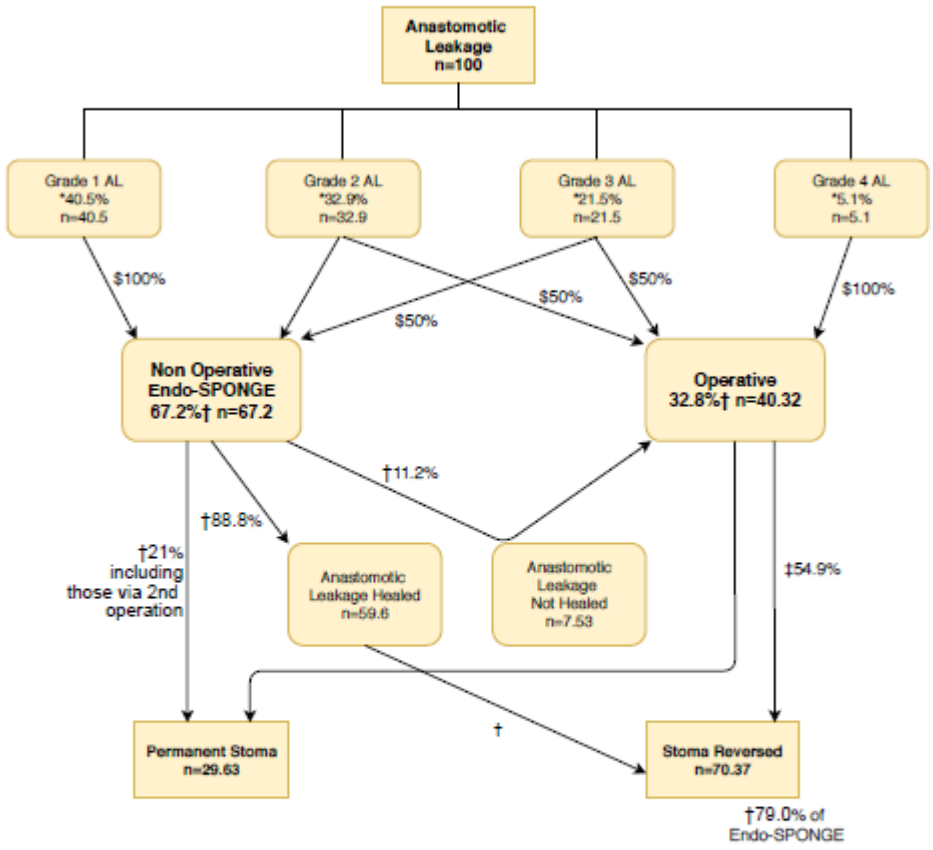
* = Asteria et al.

$ = Assumption.

† = Meta-analysis. Note: Stoma reversal figure of 52.7% on ALL current AL patients, irrespective of treatment.

.

Endo-SPONGE Process



* = Asteria et al.

$ = Assumption.

† = Meta-analysis.

‡ = Current AL data.

Current clinical outcomes

Systematic search for current outcomes following an anastomotic leak and meta-analysis of the data with forest plots are in Appendix B

Here the outcome of the systematic search and meta-analysis are discussed to present a context for the current clinical situation regarding anastomotic leak.

In total 379,022 patients with an anastomosis were included in the analysis with 27,076 patients resulting in an anastomotic leak (AL). Binary regression demonstrated a weighted mean rate of occurrence of AL of 7.8% (95% CI 6.5 to 9.1%) (I^2 = 100%).

Currently out of 19334376 (44.0%) AL are treated by non-operative means. Binary regression demonstrated a weighted mean rate of non-operative treatment of AL of 42.8% (95% CI 30.4 to 55.2%) (I^2 = 99%).

Asteria et al describe classification of AL as grades 1-4: grade 1 = limited leakage with small adjacent abscess; mild clinical symptoms, grade 2 = small lateral anastomotic failure with adjacent uni-ocular abscess (5 cm diameter or greater), grade 3 = failure of half or more of the circumference of an anastomosis and grade 4 = Multi-ocular abscess or peritonitis. Of the 79 patients with AL, 32 (40.5%) were grade 1, 26 (32.9%) were grade 2, 17 (21.5%) were grade 3, and 4 (5.1%) were grade 4 (Asteria et al. 2008). In addition, Midura et al, report that 41% of the AL were minor with the remaining 59% classified as major leaks. This data is consistent with meta-analysis and indicates that grade 1 AL are currently treated predominantly with non-operative treatments and grade 2-4 are more likely to be treated via operation depending on hospital and surgeon. For simplicity of the flow diagram for current pathway the data from Asteria has been used.

Non operative success rate was available from 6 studies covering 195 patients. From these studies 120/195 (61.5%) were successful. Binary regression demonstrated a weighted mean rate of non-operative successful healing of AL currently at 57.4% (95% CI 41.8 to 72.9%) (I^2 = 77%). Failure to heal anastomosis is assumed to then result in re-operation in the current pathway flow chart above.

Stoma reversal rate following non operative treatment was discussed in 4 studies with 34/55 (61.8%) patients successfully having their stoma reversed following non-operative treatment. Binary regression demonstrated a weighted mean rate of non-operative stoma reversal at 62.1% (95% CI 49.4 to 74.9%) (I^2 = 55%). Due to the small number of studies and patients covering current stoma reversal following non-operative treatment of AL, all current treatments for AL were analysed with regards to stoma reversal rate. Eight studies covered stoma reversal, with 275/533 (51.6%) patients successfully having their stoma reversed after an AL. Binary regression demonstrated a weighted mean rate for stoma reversal of 54.5% (95% CI 46.0 to 63.0%) (I^2 = 68%).

Current 30 day mortality following AL with all current treatments were covered in 14 papers with 1246/10,454 (11.9%) patients having 30 d mortality following AL. Binary regression demonstrated

a weighted mean rate for 30 day mortality of 10.9% (95% CI 8.0 to 13.58) (I^2 = 91%). Weighted mean could not be identified for non–operative treatment alone.

Current length of stay (LOS) following AL was reported in 10 journal articles. Continuous regression demonstrated a weighted mean LOS with AL of 25.15 days (95% CI 21.82 to 29.21 days) (I^2 = 99%). Current length of stay without AL was also analysed with continuous regression demonstrating a weighted mean without AL of 11.38 days (95% CI 9.20 to 13.56 days) (I^2 = 99%).

Of patients treated with a non-operative route 155/241 (64.3%) were treated with percutaneous drain. Binary regression demonstrated a weighted mean rate of percutaneous drain treatment (within non-operative group) of 63.8% (95% CI 41.4 to 86.1%) (I^2 = 95%).

Of patients treated with a non-operative route 140/244 (57.3%) were treated with antibiotics. Binary regression demonstrated a weighted mean rate of antibiotic treatment (within non-operative group) of 51.5% (95% CI 22.5 to 80.5%) (I^2 = 98%).

Time to stoma reversal was covered in only two studies. Mean time to healing was reported as 10.6 months (95% CI 7.55 to 13.62 months) by Harris et al and 10.23 months (95% CI 8.36 to 12.89 months) by Khan et al, (Harris et al. 2010; Khan et al. 2008).

Describe any training (for healthcare professionals and patients) and system changes that would be needed if the NHS were to adopt the technology.

The instructions for use provided in the IFU of Endo-SPONGE are detailed and no additional training measures are required for the safe use of the product in clinical practice. However training and support is available and offered by B Braun training team.

A short product/procedure overview is offered to new users, to ensure familiarity with the nuances of the treatment. While the treatment is straight forward with a short learning curve it gives the user chance to clarify anything and make sure the treatment is done as effectively and optimally as possible for the patient.

The training would involve a presentation and hands on product overview, including a non-clinical demonstration of how the treatment works and the opportunity for questions from the clinical staff.

The training is best delivered to multiple surgeons/users and nursing staff as the product is changed every 3 days, the staff administering the treatment may not be the same staff that do the 2nd, 3rd, etc. change down the line. Training multiple staff or implementing a train the trainer scheme helps benefit the colorectal unit who are administering the treatment.

In terms of system changes, the patient could be treated in the endoscopy suite instead of theatres, under mild sedation instead of general anaesthetic and as an outpatient instead of an inpatient. This is all reliant on patient health and stability and may not be applicable to all patients, as the patient improves with treatment they may move from one treatment pathway to the other, e.g. from inpatient to outpatient.

For patients once the treatment is started the patient will have a small tube coming out anally attached to the vacuum drainage bottle. Due to the vacuum the sponge will not dislodge from the cavity but they should be carefully when moving around not to pull too much on the tube and make sure the bottle is not mistreated or turned off.

4 Published and unpublished clinical evidence

Identification and selection of studies

Complete the following information about the number of studies identified.

Please provide a detailed description of the search strategy used, and a detailed list of any excluded studies, in appendix A.

Number of studies identified in a systematic search.		313
Number of studies identified as being relevant to the decision problem.		50 (20 after exclusions)
Of the relevant studies identified:	Number of published studies (included in table 1).	50 (20 after exclusions)
	Number of abstracts (included in table 2).	0
	Number of ongoing studies (included in table 3).	0

List of relevant studies

In the following tables, give brief details of all studies identified as being relevant to the decision problem.

- Summarise details of published studies in table 1.
- Summarise details of abstracts in table 2.
- Summarise details of ongoing and unpublished studies in table 3.
- List the results of all studies (from tables 1, 2 and 3) in table 4.

For any unpublished studies, please provide a structured abstract in appendix A. If a structured abstract is not available, you must provide a statement from the authors to verify the data.

Any data that is submitted in confidence must be correctly highlighted. Please see section 1 of the user guide for how to highlight confidential information. Include any confidential information in appendix

Table 1 Summary of all relevant published studies

Data source	Author, year and location	Study design	Patient population	Intervention	Comparator(s)	Main outcomes
Published study	(Arezzo et al. 2015) Italy	Retrospective Observational study	Patients following colorectal leaks treated with endoscopic vacuum therapy.	Endo-SPONGE	None	79% successful leak closure. Median duration of treatment was 12.5 sessions (range 4–40). Median time for complete healing was 40.5 days (range 8–114), for a median cost of treatment of 3.125 Euros.
Published study	(Boschetti G 2018) France	Retrospective Observational study	Patients with clinical symptomatic anastomotic leak treated by Endo-SPONGE.	Endo-SPONGE	None	Closure in 93% of patients, maintained in 89% of patients after 6 months. Mean 18.6 ± 13 Endo-SPONGE session required. 87.5 % Stoma reversal rate.
Published study	(Clifford et al. 2019)	Systematic Review	Patients with anastomotic leaks following colorectal surgery.	Endo-SPONGE	Stent, endoscopic clips, endoscopic drainage, fibrin glue	Successful leak closure for vacuum assisted closure 88.8% (range 66.6-100%).
Published study	(Huisman et al. 2019) Netherlands	Retrospective Observational study	Symptomatic anastomotic leakage after rectal surgery treated with Endo-SPONGE.	Endo-SPONGE	None	Successful leak closure 85%, bowel continuity restored 70%. 79% stoma reversal rate.
Published study	(Jimenez-Rodriguez et al. 2018) Spain	Prospective Observational case series	Patients with dehiscence of lower colorectal anastomosis or opening of the rectal stump after anterior resection for rectal cancer.	Endo-SPONGE	None	Full resolution 86%. Mean time to healing 22.3 ±14.7 days. Mean number of endoscopy sessions 3.1± 1.9. 39% stoma reversal rate.
Published study	(Katz et al. 2018) Israel	Retrospective Observational study	Patients with leaking colorectal anastomosis.	Endo-SPONGE	None	Successful leak closure for 100%. Regained bowel continuity 85%. Stoma closure in 80%. Mean number of sponge exchanges 3.6 (range 3-5). 80% stoma reversal rate.

Published study	(Keskin et al. 2015) Turkey	Prospective Observational Case series	Patients with anastomotic leak and cavity formation following colorectal surgery.	Endo-SPONGE	None	Successful leak closure 80%. Mean 2.2 sponge exchanges (range 1-5). Lumen integrity achieved 67%. 71% stoma reversal rate.
Published study	(Kuehn, Schiffmann, et al. 2016) Germany	Retrospective Observational study	Patients with use of endoscopic vacuum therapy for various lower gastrointestinal tract defects.	Endo-SPONGE	None	Anastomotic leak closure 90%, average number of sponges used 7 (range 1-37). 79% stoma reversal rate.
Published study	(Manta et al. 2016) Italy	Retrospective Observational study	Patients with different post-surgical leaks involving the gastrointestinal tract managed with endoscopy as initial approach.	Endo-SPONGE	Over-the-scope clip. Self-expanding metal stent. Fibrin glue injection.	Successful closure with Endo-SPONGE 100%.
Published study	(Milito et al. 2017) Italy	Prospective observational study	Patients with anastomotic leak and cavity formation following colorectal surgery.	Endo-SPONGE + antibiotics	None	Well tolerated with no complications
Published study	(Mussetto et al. 2017) Italy	Retrospective Observational study	Patients with anastomotic leaks following colorectal surgery.	Endo-SPONGE	None	Anastomotic leak closure 90%, mean 19 sponge changes (range 9-23). All patients with healed leak had ileostomy closed.
Published study	(Nerup et al. 2013) Denmark	Retrospective Observational study	Patients with anastomotic leak following low anterior resection of rectal cancer.	Endo-SPONGE	None	Anastomotic leak closure 100%. Stoma closure 92%. Median number of treatments 8 (range 1-18).
Published study	(Popivanov et al. 2019)	Systematic Review and meta-analysis	Patients receiving endoluminal negative pressure therapy in colorectal anastomotic leaks.	Endo-SPONGE and non Endo-SPONGE	None	Successful closure 85.4%. Stoma closure 72.6%. Median 7 sponge exchanges (range 2-34).
Published study	(Riss et al. 2009) Austria	Retrospective Observational study	Patients following surgery for low rectal cancer suffering an anastomotic leak following anterior rectal resection or leak of rectal stump following Hartmann's procedure.	Endo-SPONGE	None	Successful leak closure 66.6%.
Published study	(Riss, Stift, Kienbacher, et al. 2010) Austria	Retrospective Observational study	Patients who had undergone initially successful Endo-SPONGE assisted treatment of anastomotic leakage	Endo-SPONGE	None	Long term success after leak closed initially 75%. 87% AL closure rate and 77% stoma reversal rate.

			following rectal cancer surgery were included in the study.			
Published study	(Rottoli et al. 2018) Italy	Prospective Observational Case series	Patients with diagnosed anastomotic leak following IPAA (ileal pouch-anal anastomosis).	Endo-SPONGE	None	100% healing of leak, 88% ileostomy reversal.
Published study	(Shalaby et al. 2019)	Systematic Review and meta-analysis	Patients treated with endoluminal vacuum assisted therapy for colorectal anastomotic leakage.	Endo-SPONGE and non Endo-SPONGE	None	Successful leak closure rate 82.6%. Following successful treatment 75.9% had stoma reversed. Complication rate 13.8%.
Published study	(Srinivasamurthy et al. 2013a) UK	Retrospective Observational study	Patients with low pelvic anastomotic leakage (n=7 low anterior resection for colorectal cancer, n=1 restorative proctocolectomy for ulcerative colitis).	Endo-SPONGE	None	Complete closure or significant reduction in size of abscess 75%. Stomas reversed and good function 63%. Mean 4 sponge application (range 1-7).
Published study	(Strangio et al. 2015b) Italy	Prospective Observational Case series	Patients with anastomotic leakage following colorectal surgery, mixed reasons for surgery.	Endo-SPONGE	None	Successful leak closure 88%, complication rate 12%. Median 9 applications (range 1-39).
Published study	(Van Koperen et al. 2008) Netherlands	Prospective Observational Case series	Patients with anastomotic leak following low anterior resections for rectal cancer or restorative proctocolectomy with ileoanal pouch anastomosis for ulcerative colitis.	Endo-SPONGE	None	Cavity closure rate 56%. 56% stoma reversal
Published study	(Weidenhagen et al. 2008a) Germany	Prospective Observational Case series	Patients with anastomotic leakages after anterior resection.	Endo-SPONGE	None	Anastomotic leak healing achieved 97%, stoma closure rate 88%. Number of Endo-SPONGE applications 11 (range 1-27).

Table 2 Summary of all relevant abstracts

Data source	Author, year and location	Study design	Patient population, setting, and withdrawals/lost to follow up	Intervention	Comparator(s)	Main outcomes
N/A	N/A	N/A	N/A	N/A	N/A	N/A
N/A	N/A	N/A	N/A	N/A	N/A	N/A
N/A	N/A	N/A	N/A	N/A	N/A	N/A
N/A	N/A	N/A	N/A	N/A	N/A	N/A
N/A	N/A	N/A	N/A	N/A	N/A	N/A
N/A	N/A	N/A	N/A	N/A	N/A	N/A
N/A	N/A	N/A	N/A	N/A	N/A	N/A
N/A	N/A	N/A	N/A	N/A	N/A	N/A
N/A	N/A	N/A	N/A	N/A	N/A	N/A

No abstracts provided, all evidence submitted has been published as full Journal articles

Table 3 Summary of all relevant ongoing or unpublished studies

Data source	Author, year (expected completion) and location	Study design	Patient population, setting, and withdrawals/lost to follow up	Intervention	Comparator(s)	Outcomes
N/A	N/A	N/A	N/A	N/A	N/A	N/A
N/A	N/A	N/A	N/A	N/A	N/A	N/A
N/A	N/A	N/A	N/A	N/A	N/A	N/A
N/A	N/A	N/A	N/A	N/A	N/A	N/A
N/A	N/A	N/A	N/A	N/A	N/A	N/A
N/A	N/A	N/A	N/A	N/A	N/A	N/A
N/A	N/A	N/A	N/A	N/A	N/A	N/A
N/A	N/A	N/A	N/A	N/A	N/A	N/A
N/A	N/A	N/A	N/A	N/A	N/A	N/A

No abstracts provided, all evidence submitted has been published as full Journal articles

Table 4 Results of all relevant studies (from tables 1, 2 and 3)

Study	Results	Company comments
Arezzo et al 2015 Long-term efficacy of endoscopic vacuum therapy for the treatment of colorectal anastomotic leaks	• N=11/14 (79%) success rate closing AL leak • N=9/10 (89%) success rate for acute leaks (diagnosed <60 days post-surgery). • N=2/4 (50%) success rate for chronic leaks (diagnosed >60 days post-surgery). • N=8/8 (100%)success rate in closing AL in patients who had an initial diverting stoma • N=3/6 (50%) success rate closing AL in patients without an initial diverting stoma (3 of these patients had a stoma created after diagnosis of AL) • No significant impact on AL closure success rate with or without an initial diverting stoma (p=0.055) • N=8/10 (80%) AL closure rate in leaks that were 25% of the anastomosis • N=1/1 (100%) AL closure rate in leaks that were 50% of the anastomosis • N=2/3 (66%) AL closure rate in leaks that were 75% of the anastomosis • Median duration of treatment was 12.5 sessions (range 4–40). • Median time for complete healing was 40.5 days (range 8–114). • N=0/14 patients had complications with treatment • N=1/14 patients developed sepsis • Median abscess size 4cm (2-9cm) • 30 day mortality = 0/14 • Length of stay was 7 days for 10/14 patients • N=4/14 patients were treated as out patients for whole treatment. 10/14 patients were treated as in patient for 7 days then continued treatment as out patient • Further surgery was required in 3 cases. • Further endoscopic treatment was required for 3 cases.	Text

Table 4 Results of all relevant studies (from tables 1, 2 and 3)

Study	Results	Company comments
Boschetti et al 2018 Endo-SPONGE treatment of anastomotic leakage after colorectal surgery: A report of 29 cases compared to the main studies in the literature.	• The mean length of the fistula was 7 ± 4.6 cm (2-20cm). • The mean level from the anal verge was 6.2 ± 4.6 cm (2-20cm). • N=12/29 (41%) patients were diagnosed within 30 days of initial surgery (early diagnosis) • N=17/29 (59%) were diagnosed with AL longer than 30 days following surgery (late diagnosis) • Mean number of sessions of 18.6 ± 13 (range 4 to 57 sessions). • Median therapy duration was 70 days overall (14-196) • In the 21 patients with a stoma median treatment duration was 70 days (14-196) • In the 8 patients without a stoma the median duration of treatment was 56 days (14-98) • Successful AL closure rate was 27.29 (93%) overall • Successful AL closure rate in the stoma group was 19/21 (90%) • Successful AL closure in the no stoma group was 8/8 (100%) • No correlation to time of AL discovery and closure (Rho=0.45 p=0.12) • Stoma reversal was achieved in 18/21 (87.5%) patients • Stoma reversal was achieved with 6 month for those reversed. • N=0/29 patients reported during treatment. • Twelve patients (41%) were under antibiotics when Endo-SPONGE was performed, after a few days (less than 10), the antibiotics can be stopped. • All (29/29) patients were treated as out patients • Long term success was achieved 24/29 (83%) patients • One patient required extra surgery.	
Clifford et al 2010 Early anastomotic complications in colorectal surgery: a systematic review of techniques for endoscopic salvage	• The overall rate of anastomotic salvage in patients without generalised peritonitis. • Stent range = 50-100%. • Endoscopic clips = 57.1-100%. • VAC = 88.8% (range 66.6–100%), with very few adverse outcomes reported. • Endoscopic drainage = 78.5%. • Fibrin Glue = not clear.	Text

Huisman 2019 et al Effectiveness of Endo-SPONGE therapy for the management of presacral abscesses following rectal surgery				Previous studies reported a persistent sinus rate at 1 year of 48% after anastomotic leakage without Endo-SPONGE therapy.

	Total group	Early endosponge	Late endosponge	*p* value
Days until anastomotic leak detection[b]	12 [3–67]	10 [3–19]	21 [4–67]	0.10[c]
Days until first endosponge[b]	21 [5–537]	11 [5–20]	30 [21–537]	< 0.001[c]
Endosponge changes[b]	9 [2–28]	6 [2–28]	14 [2–26]	0.45[c]
Duration endosponge therapy (days)[b]	25 [3–115]	20 [3–115]	25 [5–80]	0.79[c]
Median follow-up (months)[b]	10 [3–84]	8 [3–25]	12 [6–84]	0.08[c]
Success endosponge therapy[a]	17 (85)	8 (80)	9 (90)	–
Restored continuity[a]	14 (70)	7 (70)	7 (70)	–
Time until stoma reversal[b]	10 [3–15]	7 [3–11]	10 [6–15]	0.15[c]
Chronic sinus[a]	3 (15)	2 (20)	1 (10)	–

[a]Count (%), [b]Median [range], [c]Mann–Whitney *U*

- N=14/20 Patients were diverted during initial surgery, n=4 were diverted after AL diagnosis.
- Median distance of AL from anal verge 8.5 cm (5-12cm)
- Group split into early and late based around median time to treatment N=10/20 in each group.
- Median 9 sponge changes (2-28)
- Endo-SPONGE successful (closed leak) in 17/20 (85%) of patients.
- Similar success in early group (n=8/10 AL closure) and late group (n=9/10 AL closure)
- Stoma was reversed in n=14/18 (78%) of patients
- Time to stoma reversal median 10 months over all (3-15). Median 7 months in early group (3-11). Median 10 months in late group (6-15). No significant different between time to treatment and time to stoma reversal (p=0.15).
- 14/20 patients (70%) bowel continuity was restored. (8/10 (80%) with early treatment , 9/10(90%) with late treatment)
- The overall cumulative probability of Endo-SPONGE therapy success was 88% (95% CI = 57–97%).
- The overall cumulative probability of stoma reversal was 73% (95% CI = 44–87%).
- The overall cumulative probability of stoma reversal for patients in the early Endo-SPONGE group was 77% (95% CI = 22–93%) compared with 70% (95% CI = 23–88%) for patients in the late Endo-SPONGE group. This difference in absolute risks was not statistically significant (p = 0.31).
- A chronic sinus occurred in 15% of the patients in our study.
- N=0/20 patient dies within 30 days
- Extra surgery required in n=6/20 (30%)

Table 4 Results of all relevant studies (from tables 1, 2 and 3)

Study	Results	Company comments
Jimenez-Rodriguez et al 2018 A New Perspective on Vacuum-Assisted Closure for the Treatment of Anastomotic Leak Following Low Anterior Resection for Rectal Cancer, Is It Worthy?	• All patients had a stoma following Hartmann's and LAR surgery. • N=15/22 (68%) patient treated 'early' (within 6 weeks), the remaining 7/22 (32%) were treated 'late' (after 6 weeks) • The mean time to achieve healing was 22.3 ± 14.7 days; 24.0 ± 15.5 days for the anterior resection group and 19.8 ± 14.09 days for the Hartmann group. • The mean distance of the anastomosis from the anal margin was 4.92 ± 1.9 cm. Rectal stumps were 3.90 ± 2.4 cm above the dentate line. • Average length of the cavity measured at the beginning of the treatment was 5.90 ± 1.9 cm; 5.3 ± 1.8 cm in the anterior resection group and 6.6 ± 2.1 cm in the Hartmann group. • VAC treatment < 6 weeks n=15/20. • The mean number of endoscopic sessions per patient was 3.1 ± 1.9 in the anterior resection group and 3.2 ± 1.8 in the Hartmann group. • N=19/22 successful for AL closure • Onset of therapy < 6 weeks significant impact on success rate over treatment after 6 weeks (p=0.041, no extra data). Cavity size impact treatment success (p=0.226) no extra data • Stoma reversed in 5/13 patients with stoma (39%) • The mean time to achieve healing was 22.3 ± 14.7 days; 24.0 ± 15.5 days for the anterior resection group and 19.8 ± 14.09 days for the Hartmann group. • N=4/22 (18%) recurrence of cavity (re-treated with Endo-SPONGE and n=3/4 (75%) then healed). • After final sponge removal n=10/22 (45%) fibrin glue added. • N=1/22 patient treated with antibiotics in addition to Endo-SPONGE. • Bowel continuity achieved in n=5/13 (39%) patients. • N=0/22 patient died within 30 days. Long term follow up rate mortality rate of 3/22 • Half (n=11/22) patients treated as out patients. • N=4/22 patient required a second course of Endo-SPONGE for long term success • Overall long term success after 1 or 2 round of Endo-SPONGE treatment n=18/22 (82%) • N=2/22 (9%) patients required extra surgery	Text

Table 4 Results of all relevant studies (from tables 1, 2 and 3)

Study	Results	Company comments
Katz et al 2018 Different approaches for Endo-SPONGE® insertion to treat rectal anastomotic leaks	• Half (n=3/6) patients had initial diverting stoma • A diverting stoma was constructed in two out of the three patients who had no previous diversion. • All patients were diagnosed within 14 days and treated within 17 days • All N=6/6 patients had successful AL closure • N=4/5 (80%) patients with a diverting stoma underwent closure of their stoma (N=1/5 patient was scheduled for ileostomy closure, at surgery a large desmoid tumour was found. Tumour did not allow a safe ileostomy closure and the procedure was aborted). • N=0/6 mortality rate within 30 days • The mean number of Endo-SPONGE exchanges was 3.6 (range 3–5 exchanges). • One patient was treated with Endo-SPONGE and antibiotics with no need for diversion. • Sepsis control was achieved following the initial treatment (antibiotics, Endo-SPONGE, and diversion). • All patients fully recovered and were discharged following completion of treatment. • Median duration of follow-up was 28 months (range 18–32 months). • N=5/6 (83%) regained bowel continuity. • Despite a wide range of anastomotic dehiscence (up to 270°), we achieved good results with anastomosis preservations in all patients. **Table 1** Patient data | Pt | Age (years) | Etiology | Operation | Diverting stoma at index surgery | Diverting stoma following leak | Anastomosis type and height | Day of leak diagnosis | Dehiscence range (degrees) | First endosponge insertion (days) | |---|---|---|---|---|---|---|---|---|---| | 1 | 77 | Low rectal cancer | Laparoscopic LAR | Yes | _ | Coloanal hand-sewn | 8 | 70 | 33 | | 2 | 69 | Rectal villous adenoma | Laparoscopic AR | No | Yes | Stapled, 7 cm from anal verge | 4 | 210 | 13 | | 3 | 22 | Hirschsprung | Open re- AR | Yes | _ | Coloanal hand-sewn | 6 | 270 | 11 | | 4 | 38 | Familial adenomatous polyposis | Total proctocolectomy + J pouch anal anastomosis | Yes | _ | Coloanal hand-sewn | 7 | 180 | 9 | | 5 | 63 | Ovarian cancer with rectal involvement | Open AR + TAH | No | No | Stapled, 10 cm from anal verge | 14 | 50 | 17 | *Pt* patient, *LAR* low anterior resection, *AR* anterior resection, *TAH* total abdominal hysterectomy	Text

Table 4 Results of all relevant studies (from tables 1, 2 and 3)

Study	Results	Company comments
Keskin et al 2015 Effectiveness of Endoluminal Vacuum-assisted Closure Therapy (Endo-SPONGE) for the Treatment of Pelvic Anastomotic Leakage After Colorectal Surgery	• N=8/15 patients were treated 'early' (within 30 days, median 15 days range 6-27) and N=17/15 patients were treated 'late' (more than 30 days, median 173, range 43-343) • N=12/15 (80%) successful closure of AL overall • N=6/8 (75%) successful AL closure in early treatment • N=6/7 (85%) successful AL closure with late treatment • N=14/15 patients had a stoma created. • Stoma reversal in N=10/14 (n=3 died due to disease progression before reversal) • N=12/15 (80%) lumen integrity achieved. • N=10/14 (71%) stoma patients n=3/14 patients deceased before able to close stoma. • Average 2.2 Endo-SPONGE applications (range 1-5). • N= 2/15 discontinued due to progressing pelvic sepsis and n=1 discontinued due to bleeding. • N=0/15 recurring abscess. • Extra surgery was required for N=3/15 patients. • 30 day mortality rate was 0/15, long term 3/15 patients dies due to disease progression	Text

Table 4 Results of all relevant studies (from tables 1, 2 and 3)

Study	Results	Company comments
Kuehn et al 2016 Endoscopic Vacuum Therapy in Colorectal Surgery		

Group	*n*	Duration of therapy	Number of sponges	Success
Total	41	20 (2–131)	6 (1–37)	34/41 (83 %)
Anastomotic leakage	20	23 (2–109)	7 (1–37)	18/20 (90 %)
Rectal stump insufficiency	12	12 (3–131)	4 (2–26)	9/12 (75 %)
Others	9	20 (3–43)	6 (1–12)	8/9 (89 %)

- Median number of sponges inserted = 6 (range 1-37).
- Mean changing interval of 3 days (range 1-5).
- Median therapy time 20 days (range 2-131).
- Sucessful with local control of septic focus in N=34/41 (83%).
- Successful closure of leak in n=18/20 (90%).
- Median duration of therapy 23 days (range 2-109).
- Median number of sponge insertions of seven (range 1–37).
- A protective enterostomy created in 19 of 20 patients. Closure of protective enterostomy was possible in 15 of 19 patients (79%).
- Median time to closure of enterostomy was 244 days (range 152–488). Closure of enterostomy was not possible in n=4/19 patients due to the (n=2 failure / discontinuation of EVT, n=1 multi-morbidity and n=1 sphincter insufficiency).
- Complications /adverse event occurred in n=4/20 patients (n=1 bleeding, n=3 stenosis)
- 30 day mortality was 0/20

Manta 2016 Endoscopic management of patients with post-surgical leaks involving the gastrointestinal tract: a large case series	• Median abscess size 3 cm (1.5-5cm) • OTSC positioning alone N=39. • Self-expanding metal stent (SEMS) N=7. • Endo-SPONGE application N=7. • OTSC + SEMS N=21. • OTSC + Fibrin glue N=1. • SEMS = Fibrin glue N=1. • N=7 Endo-SPONGE treatments. • N=7/7 complete closure achieved with Endo-SPONGE treatment. • N=7/7 no other therapy or intervention required. • Mean diameter = 29 cm (range 15-50). • N= 6/7 delayed onset, n=1/7 early onset. • (Table only covering Endo-SPONGE section of table). • 0/7 mortality rate • 7/7 treated as out-patient – no length of stay. • 0/7 additional surgery required • 0/7 additional endoscopic treatment required Table 2. Patients with anastomotic leaks involving the colon | N	Surgery	Fistula type	Diameter (mm)	Endoscopic therapy*	Success (yes/not)	Other therapy	Final outcome
1	Anterior rectal resection	Early	10	OTSC (1)	Yes	Not	Closure
2	Anterior rectal resection	Delayed	5	OTSC (1)	Yes	Not	Closure
3	Anterior rectal resection	Delayed	30	Endo-sponge	Yes	Not	Closure
4	Anterior rectal resection	Delayed	30	Endo-sponge	Yes	Not	Closure
5	Anterior rectal resection	Delayed	6	OTSC (1)	Yes	Not	Closure
6	Anterior rectal resection	Early	50	OTSC (2) + SEMS (1)	Not	Open re-intevention	Miles' resection
7	Anterior rectal resection	Early	50	OTSC (2) + SEMS (1)	Not	Open re-intevention	Miles' resection
8	Anterior rectal resection	Delayed	15	Endo-sponge	Yes	Not	Closure
9	Anterior rectal resection	Early	10	OTSC (1)	Yes	Not	Closure
10	Anterior rectal resection	Early	5	OTSC (1)	Yes	Not	Closure
11	Anterior rectal resection	Early	5	OTSC (1)	Yes	Not	Closure
12	Anterior rectal resection	Delayed	30	Endo-sponge	Yes	Not	Closure
13	Anterior rectal resection	Early	20	OTSC (2) + SEMS (1)	Yes	Radiological drainage	Closure
14	Anterior rectal resection	Early	10	OTSC (2)	Yes	Radiological drainage	Closure
15	Left colectomy	Delayed	20	Endo-sponge	Yes	Not	Closure
16	Left colectomy	Early	50	Endo-sponge	Yes	Not	Closure
17	Left colectomy	Early	20	OTSC (1) + SEMS (1)	Yes	Not	Closure
18	Left colectomy	Early	20	OTSC (2)	Not	Radiological drainage	Open re-invention
19	Right colectomy	Delayed	10	OTSC (1)	Yes	Not	Closure
20	Right colectomy	Delayed	30	OTSC (2)	Not	Radiological drainage	Open re-invention
21	Right colectomy	Delayed	15	OTSC (1)	Not	Laparoscopic suturing	Closure
22	Total colectomy	Delayed	30	Endo-sponge	Yes	Not	Closure
23	Total colectomy	Delayed	25	OTSC (2)	Not	Radiological drainage	Open re-invention
24	Hartmann's resection	Delayed	5	OTSC (1)	Yes	Not	Closure
25	Prostatectomy	Delayed	10	OTSC (1)	Yes	Not	Closure
26	Prostatectomy	Early	5	OTSC (1)	Yes	Not	Closure
27	Prostatectomy	Delayed	5	OTSC (1)	Yes	Not	Closure
28	Cystectomy	Delayed	7	OTSC (1)	Yes	Not	Closure
29	Cystectomy	Delayed	15	OTSC (2)	Not	Open re-intervention	Nephrostomy
*SEMS: Self-expandable metallic stent (number of device used); OTSC: over-the-scope clip; Endo-sponge: open-pored polyurethane sponge.							

Table 4 Results of all relevant studies (from tables 1, 2 and 3)

Study	Results	Company comments
	Table 3. Outcome of fistula treatment according to devices used Device used / Patients treated / Fistula closure (%) OTSC / 39 / 33 (84.6) SEMS / 7 / 5 (71.4) Endo-sponge / 7 / 7 (100) OTSC + SEMS / 21 / 17 (80.9) OTSC + Tissucol / 1 / 0 SEMS + Tissucol / 1 / 1	
Milito et al 2017 Endoluminal Vacuum Therapy as Treatment for Anastomotic Colorectal Leakage.	• All patient n=14/14/ were treated with antibiotics as well as Endo-SPONGE • Median abscess size 8.1 cm x 4.6 cm • All patients n=14/14 treated as an out patient • All patient n=14/14 had a protective stoma created with initial surgery. • All AL were detected within 7-21 days following surgery • The median duration of the outpatient therapy was 35 days (range 16–51), with 3–14 sponge exchanges for each patient. • Median healing time was 37 days (range 19–55). • The cavity from the anastomotic leakage was photographed at each change of sponge • No intraoperative complications were recorded. None of the patients required a transanal suturing to close the defect. • The Endo-SPONGE® device was well tolerated by all patients, and specific side effects during or after the therapy were not observed. • Five cases of mild anal pain successfully treated medically.	

Table 4 Results of all relevant studies (from tables 1, 2 and 3)

Study	Results	Company comments
Mussettos et al 2017 Long-term efficacy of vacuum-assisted therapy (Endo-SPONGE®) in large anastomotic leakages following anterior rectal resection	Table 1 Patient characteristics and clinical data	

Patient N°	Age	No. of Endo-SPONGE® treatments	Endo-SPONGE® treatment to closure (days)	Distance of anastomosis from anal verge (cm)	Size of leakage (cm)	Closure of anastomotic leakage	Relapse of leakage	Complication	Follow up (months)
1	81	19	41	6	8	Yes	No	No	40
2	68	9	18	6	5	Yes	No	No	64
3	74	21	47	3	10	Yes	No	No	12
4	51	10	22	3	8	Yes	No	No	19
5	76	15	65	5	8	Yes	No	Stenosis	51
6	66	20	33	5	6	Yes	No	No	46
7	55	23	51	2	5	No	-	-	-
8	70	13	28	8	4	Yes	No	No	18
9	79	9	24	4	12	Ye s	No	No	9
10	82	20	44	3	8	Yes	No	Stenosis	21
11	82	18	37	4	9	Yes	No	No	6
Total	71	16	37.3	4.5	7.5	10/11 (90.9%)	None	2/11 (18%)	28.6

- Median abscess sixe 7.5cm (4-12)
- Median distance from anal verge 4.5 cm (2-8)
- N=10/11 (90.0%) showed anastomotic closure after mean of 16 (range 9-23) sponge changes performed over a mean of 37 (range 18-65) days.
- Long term success achieved in N=10/10 healed AL
- The ileostomy was subsequently closed in all the 10 patients with a closed abscess cavity.
- Extra surgery required in N=1/11 (9%) converted to a Hartmann's
- There were 2 cases (18%) of anastomotic stricture
- N=1/11 (95) patient required a further stent fitted endoscopically
- 30 day mortality rate 0/11, long term mortality 2/11 (18%)

Table 4 Results of all relevant studies (from tables 1, 2 and 3)

Study	Results	Company comments
Nerup et al 2013 Promising results after endoscopic vacuum treatment of anastomotic leakage following resection of rectal cancer with ileostomy	• N=13/13 successful healing of anastomotic cavity. • N=12/13 (92%) stoma closure rate of the entire study group. • Median length of stay in hospital 25 days (7-39). • Some continued treatment in an outpatient setting. • Median number of treatments 8 (1-18). • Endo-SPONGE treatment lasted a median of 18 days (3-40). • Median length of stay was 25 days (7-39) • N=1/13 cases of stenosis (7.6%) • Extra surgery was required in n=1/13 • N=2/13 patient were moved to conservative treatment • 30 day mortality N=0/13	

Popivanov et al 2019 Endoluminal negative pressure therapy in colorectal anastomotic leaks	• A total of 295 cases were analysed. • The follow-up was between 2 and 36 months. • The median distance of the anastomosis from the anal verge and the size of the abscess were 5.65 cm (4.9–10) and 6.0 cm (5–8.1) respectively. • In 84.5% (78%–91%) of cases the stoma was created during the first intervention. • NR was performed in 48.6% (3%–60%) of the cases, but its type (short-term or long-term course) was not addressed in the studies. • A median of 7 sponges (2–34) were used. • A median negative pressure of 150 mmHg (125–700) for a median of 31 days (14–127). • The success rate was 85.4% (80%–91%). • Ileostomy closure was achieved in 72.6%. • Complications were observed in 19% (13%–25%). • Abscess was the most frequent complication (11.5%), followed by stenosis of the anastomosis (4.4%). • Laparotomy was required in 3% of all cases and in 15% of the complications. • There was statistical proof for significant association with the success of ENPT only for the stoma (0.007, SE 0.004, P = 0.040). • The remaining explored variables were not significantly associated with the success of ENPT: • Number of treatment days (-0.002, SE 0.001, P = 0.162). • Number of sponges used during therapy (0.006, SE 0.005, P = 0.215) Number of NRs (-0.002, SE 0,006, P = 0.770) **Table I** The descriptive analysis of ENPT in insufficiency of low colorectal anastomoses. | Study | Year | *n* | Stoma | | Days | Sponges, *n* | Success | | | | | | *n* | % | | | *n* | % | | Nagell *et al.* [29] | 2006 | 4 | 4 | 100 | 51 | – | 4 | 100 | | Weidenhagen *et al.* [30] | 2008 | 29 | 25 | 86 | 34 | 11 | 28 | 96 | | Mees *et al.* [31] | 2008 | 5 | 5 | 100 | 28 | 7 | 5 | 100 | | Van Koperen *et al.* [24] | 2009 | 16 | 16 | 100 | 40 | 13 | 9 | 56 | | von Bernstorff *et al.* [13] | 2009 | 26 | 18 | 69 | 50 | 10 | 23 | 89 | | Riss *et al.* [11] | 2010 | 17 | 13 | 77 | 21 | 7 | 12 | 71 | | Verlaan *et al.* [33] | 2011 | 6 | 5 | 83 | 14 | 3 | 5 | 100 | | Nerup *et al.* [28] | 2013 | 13 | 13 | 100 | 18 | 8 | 13 | 100 | | Veloso *et al.* [36] | 2013 | 1 | 0 | 0 | 75 | 34 | 1 | 100 | | Srinivasamurthy *et al.* [26] | 2013 | 8 | 8 | 100 | 21 | 4 | 6 | 75 | | Arezzo *et al.* [25] | 2015 | 14 | 8 | 57 | 41 | 13 | 11 | 79 | | Strangio *et al.* [34] | 2015 | 25 | 13 | 52 | 28 | 9 | 22 | 88 | | Keskin *et al.* [27] | 2015 | 15 | – | – | – | 2 | 12 | 80 | | Kuehn *et al.* [7] | 2016 | 20 | 19 | 95 | 23 | 7 | 18 | 90 | | Milito *et al.* [32] | 2017 | 14 | 14 | 100 | 37 | (3–14) | – | – | | Jimenez-Rodriguez *et al.* [35] | 2018 | 13 | 13 | 100 | 24 | 3 | 10 | 77 | | Boschetti *et al.* [8] | 2018 | 29 | 21 | 72 | 70 | 19 | 27 | 93 | | Borstlap *et al.* [3] | 2018 | 30 | 20 | 67 | 127 | 3.5 | 21 | 70 | | Mencio *et al.* [9] | 2018 | 10 | 9 | 90 | 24 | 6 | 6 | 60 | | Total†, median (range) | – | 295 | 224/280 | 84.5 | 31 (14–127) | 7 (2–34) | 233/281 | 85.4 | *n*, patients; days, days of treatment; success, complete closure of the abscess cavity. †The proportions are based on the random analysis; the continuous variables are presented as median values.	

Table 2 Descriptive analysis of the secondary outcome variables.

Study	*n*	cm	NR *n*	NR %	mmHg	Abscess size (cm)	Stoma closure *n*	Stoma closure %
Nagell *et al.* [29]	4	–	1	25	125	–	–	–
Weidenhagen *et al.* [30]	29	5.3	9	31	–	–	22/25	88
Mees *et al.* [31]	5	(4–7)	0	0	166	6.5	1/5	20
Van Koperen *et al.* [24]	16	5	11	68	–	–	5/16	31
von Bernstorff *et al.* [13]	26	–	14	54	–	–	–	–
Riss *et al.* [11]	17	–	6	35	–	–	13/14	76
Verlaan *et al.* [33]	6	–	1	17	–	–	5/5	100
Nerup *et al.* [28]	13	9	6	46	–	–	12/13	97
Veloso *et al.* [36]	1	10	1	100	–	6.0	–	–
Srinivasamurthy *et al.* [26]	8	–	6	75	–	–	5/8	62
Arezzo *et al.* [25]	14	–	7	50	(700–200)	5.0	–	–
Strangio *et al.* [34]	25	–	8	32	150	5.6	11/13	85
Keskin *et al.* [27]	15	–	–	–	–	–	10/14	71
Kuehn *et al.* [7]	20	–	15	75	125	–	15/19	79
Milito *et al.* [32]	14	3–7	–	–	–	8.1	–	–
Jimenez-Rodriguez *et al.* [35]	13	4.9	–	–	150	5.9	5/13	38
Boschetti *et al.* [8]	29	6.3	19	66	125	7.0	18/21	86
Borstlap *et al.* [3]	30	–	22	73	–	–	20/30	67
Total†, median (range)	285	5.65 (4.9–10)	126/243	48.6	150 (125–700)	6.0 (5–8.1)	142/196	72.6

NR, neoadjuvant radiotherapy.
†The proportions are based on the random analysis; the continuous variables are presented as median values.

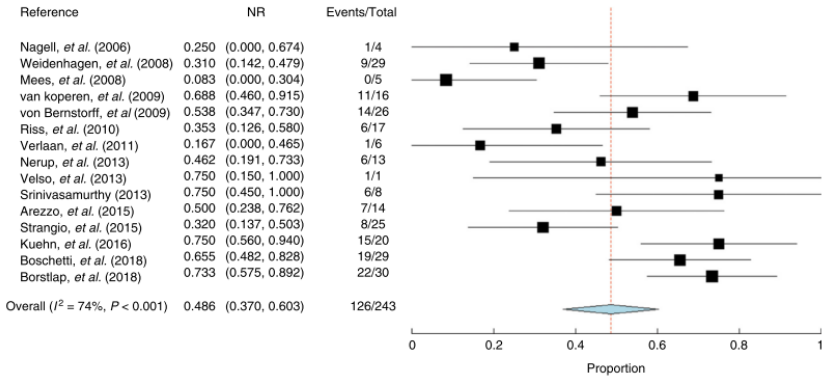


Figure 2 Neoadjuvant therapy (NR).

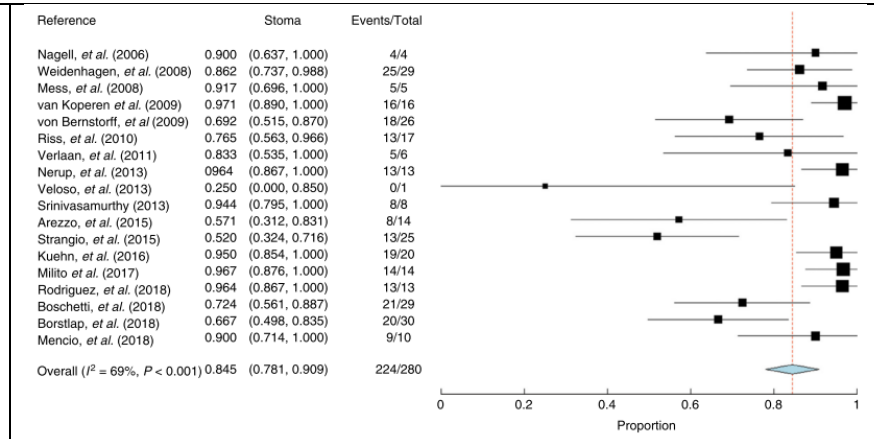


Figure 3 Stoma rate.

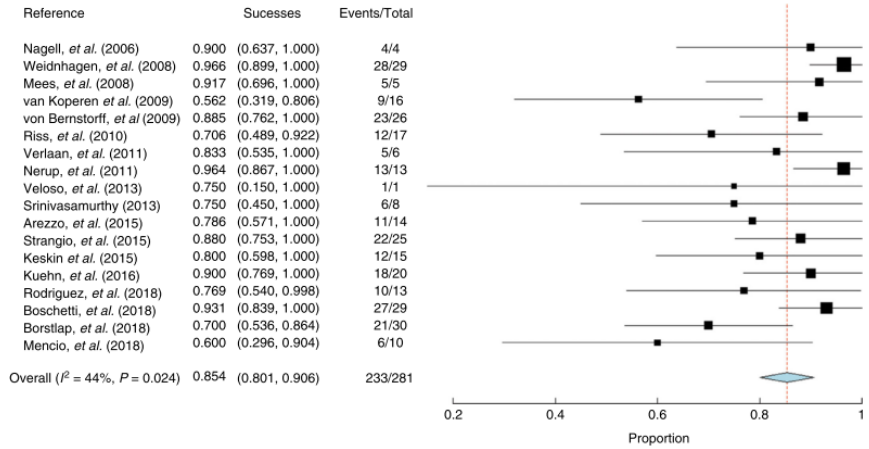


Figure 4 Success rate.

Table 4 Results of all relevant studies (from tables 1, 2 and 3)

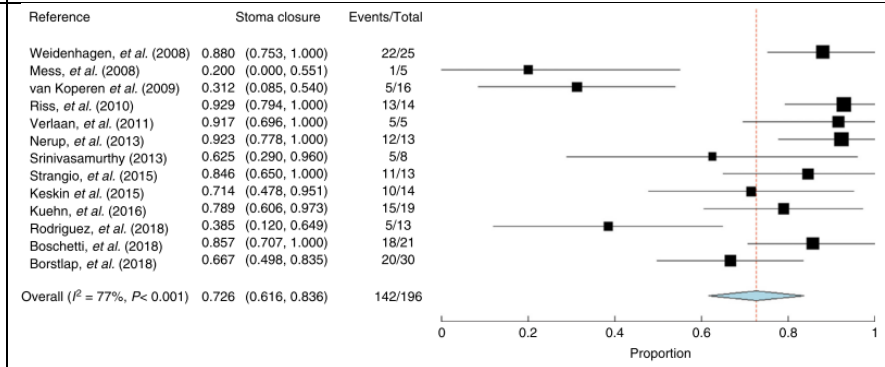
Study	Results	Company comments
		

Figure 5 Stoma closure rate.

Table 4 Results of all relevant studies (from tables 1, 2 and 3)

Study	Results	Company comments
Riss et 2009 Endo-SPONGE assisted treatment of anastomotic leakage following colorectal surgery	• Initially n=1/6 AL resulting from LAR had a protective stoma, (all Hartmann's have a stoma created). N=3 patient were further diverted following AL diagnosis • N=1/9 (11%) patient were treated early, within 7 days • N=8/9 (89%) patient were treated for AL 'late' median of 2.5 months after surgery (1-24) • N=6/9 (66.6%) healed overall • N=5/6 AL leak were healed (89%) • N=1/3 Hartmann's leak healed (33%) • N=3/9 (33.3%) no response and required surgery. • N=5/6 (83.3%) healed for anastomotic leak after rectal resection (n=1/6 required surgery). • N=1/3 (33.3%) healed after rectal stump leakage after Hartmann's procedure (n=2/3 required surgery). • The total time of Endo-SPONGE treatment was a median of 3 weeks (range 2–8). • The median duration of each Endo-SPONGE replacement was 15 min (range 5– 65). • One patient died during hospitalisation because of a heart attack. • The Endo-SPONGE application was changed every 2–3 days. • Patients satisfaction VAS 0 = best, 10 = worst. • Patient satisfaction, median = 3 (range 0-9). • Alteration in daily life, median = 5 (range 1-9). • Pain, median = 3 (range 0-6). • N=0/9 complications • 30 day mortality N=1/2 had a heart attack. • Extra surgery was required for N=3/9 (33%) patients	

Table 4 Results of all relevant studies (from tables 1, 2 and 3)

Study	Results	Company comments
Riss et al 2010 Recurrent abscess after primary successful Endo-SPONGE treatment of anastomotic leakage following rectal surgery	• N=14/23 patients had a diverting stoma with initial surgery. • N=2/9 patient without an initial stoma were diverted upon diagnosis of AL • Median 21 days of treatment (7-106) • N=20/23 Endo-SPONGE treatments initially successful (87%). • Long term success achieved in 15/20 patients with initial success - Extra surgery required in N=3/20, CT guided drainage required in N=1/20 patients • Stoma reversed in N=13/17 (76.5%) • N=6/23 (30%) patients developed long term complications N= developed recurrent symptomatic abscess and N=1 stenosis • 30 day mortality n=0/23, long term mortality n=4/23 • Median interval between primary operation and onset of anastomotic leakage was longer in the non-successful group ($P < 0.05$).	
Rottoli et al 2018 Endoluminal vacuum-assisted therapy as treatment for anastomotic leak after ileal pouch-anal anastomosis: a pilot study	• Anastomotic leak was diagnosed at a median of 14 (6–35) days after surgery. • All leaks were symptomatic. In particular, signs of sepsis were observed in all cases (fever, leucocytosis, and tachycardia). • The Endo-SPONGE treatment started at a median of 6.5 (1–15) days after diagnosis of the leakage. • Treatment lasted for a median of 12 (3–32) days. • The device was replaced a median of 3 (1–10) times. • The median length of hospital stay after the first application of the treatment was 15.5 (6–48) days. • Overall, the median length of hospital stay (including the postoperative stay from the pouch surgery in seven cases and the closure of ileostomy in one case) was 32 (16–72) days. • The complete healing of the leak was documented after a median of 60 (24–90) days from the first treatment. • Complete leak healing occurred in all 8/8 (100%) patients. • All patients but one (n=7/8, 87.5%) had their ileostomy reversed at a median of 2.5 (1–6) months from the endoscopic confirmation of healing. • The patient who retained the ileostomy chose to delay the closure for personal reasons. However, a contrast enema confirmed the closure of the defect. • At a median follow-up time of 11.6 (6–18) months after confirmation of the healing of the anastomotic leak, no recurrence was documented. • No patients reported incontinence to faeces or gas. • 30 day mortality N=0/8 • All patients were treated as in patients	

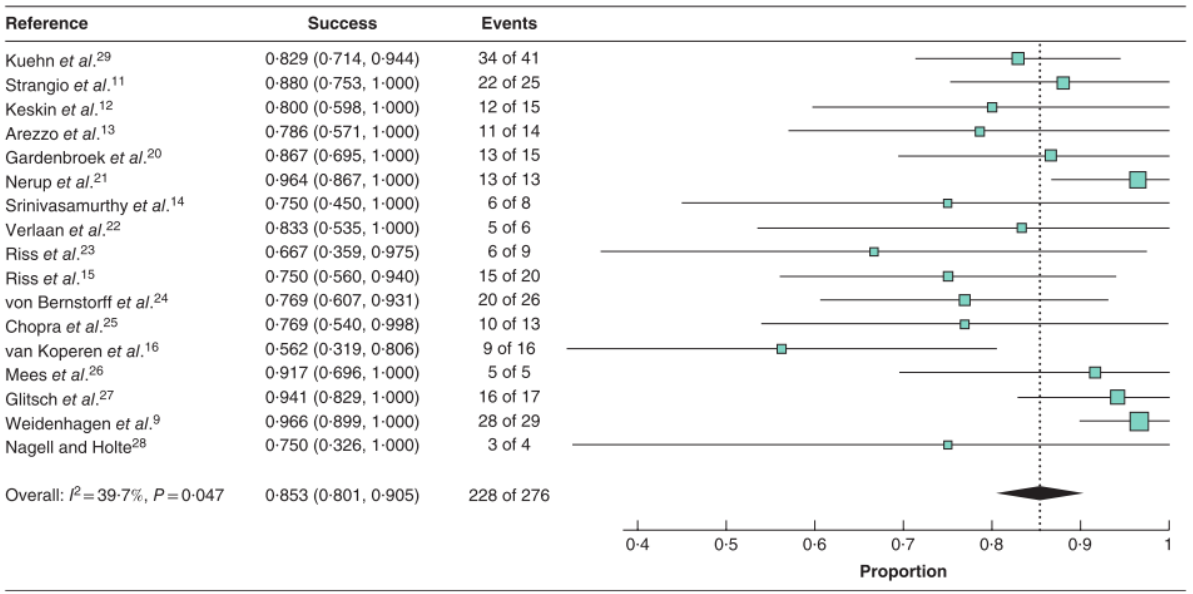
Shalaby et al 2019 Systematic review of endoluminal vacuum-assisted therapy as salvage treatment for rectal anastomotic leakage	• N=228/276 (82.6%) patients healed with endoscopic vacuum therapy.  **Fig. 3** Forest plot for success rate of endoluminal vacuum-assisted therapy across the studies. A random-effects model was used for meta-analysis. Success rates are shown with 95 per cent confidence intervals • Random-effects meta-analysis showed that the weighted mean success rate of EVT was 85·3 (95 % CI 80·1-90·5) % (I^2 =39·7 %) P=0.047 • A total of 141 patients had faecal diversion. • N=107/141 underwent reversal of stoma following successful treatment.	

Table 4 Results of all relevant studies (from tables 1, 2 and 3)

Study	Results	Company comments

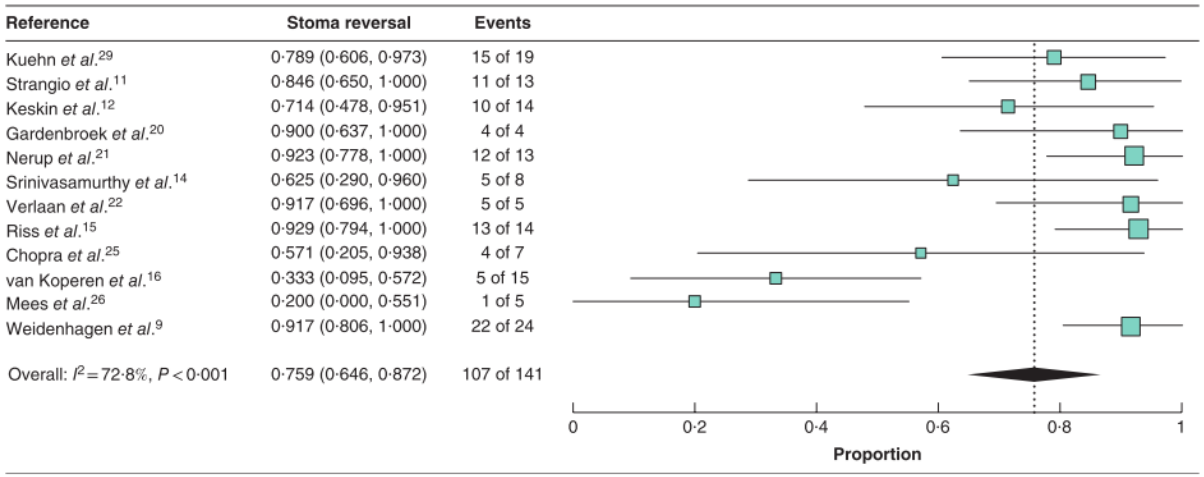


Fig. 4 Forest plot for stoma reversal rate after endoluminal vacuum-assisted therapy across the studies. A random-effects model was used for meta-analysis. Stoma reversal rates are shown with 95 per cent confidence intervals

- Random-effects meta-analysis showed the weighted mean rate of stoma reversal across the studies to be 75·9 (95 % CI 64·6-87·2) % (I^2 =72·7 %) P<0.001.

- EVT is a promising, minimally invasive treatment for anastomotic leakage following rectal resection. With a mean success rate of 85 %, the need for additional surgery could be reduced significantly.
- Compared with the current literature, which reports a stoma reversal rate of 30–40 % for clinical leakage, the weighted mean rate of stoma reversal across the studies was 75·9 %.
- Optimal results may be achieved when endoscopic EVT is offered to patients with distal anastomotic leakage who already have a defunctioning stoma, without sepsis.
- EVT has a good safety profile with a mean complication rate of approximately 14 %. Stenosis is the most common complication, and may be caused by anastomotic leakage rather than by EVT.

Table 4 Results of all relevant studies (from tables 1, 2 and 3)

Study	Results	Company comments
Srinivasamurthy et al 2013 An initial experience using transanal vacuum therapy in pelvic anastomotic leakage	• AL diagnosis was a median of 29 days (10-115) following initial surgery • Initial sponge was placed 'early' (<6 weeks) for N=3/8 patients and 'late' (> 6 weeks) N=5/8 patients • Complete closure or reduction in size of abscess N=6/8 (75%) • Extra surgery was required for N=2/8 (25%) • Ileostomies reversed N=5/8 – function was described as 'good' in all reversals • Time to stoma reversal median of 41 months (10-45) • Bowel continuity was achieved in N=5/8 (62.5%0 patients • N=5 started Endo-SPONGE < 6 weeks, n=4/5 (80%) achieved bowel restoration with good results. • N=3 started Endo-SPONGE treatment > 6 weeks, n=1/3 (33%) achieved bowel restoration with good results. • Median number of sponge applications was 4 (range 1–7), over a median treatment period of 26 days (range 7–49 days). • N=1 complication of 'inadvertent placement of Endo-SPONGE'	

Table 4 Results of all relevant studies (from tables 1, 2 and 3)

Study	Results	Company comments
Strangio et al 2015 Endo-SPONGE therapy for management of anastomotic leakages after colorectal surgery: A case series and review of literature	• N= 22/25 (88%) patient fully healed anastomotic leakage with sole use of Endo-SPONGE. • Stoma reversed for N=11/13 (84%) • 3/25 (12%) developed complications. N=1 uretheric fistula, n=1 ileal fistula, n=1 pararectal abscess. • The anastomotic leakage extension ranged from near 70 to 270 degrees of the whole anastomotic circumference. • Median abscess size 5.6 cm (1.5-10.0) • The anastomotic leak was detected after a median of 17 days (range 0–102 days) after the surgical intervention, with a median o 16 days (0-53) from diagnosis of AL to sponge placement • The Endo-SPONGE treatment was applied after a median of 16 days (range 0–53 days) from anastomotic leakage detection. • A median of one (range 1–3) sponges were used in the first session. • The median number of applications per patient was 9 (1–39 applications). • Treatment duration of 4 weeks (range 1–32). • One patient who developed an ileal fistula received only 1 Endo-SPONGE treatment before undergoing surgical re-intervention. • All patients well tolerated Endo-SPONGE permanence during the treatment interval. • There was no dislocation of the sponge system under continuous vacuum therapy. • Extra surgery required for N=2/25 (8%) • Additional CT guided drainage required for N=1/25 (4%) • 2 patients were also on antibiotics	

Table 4 Results of all relevant studies (from tables 1, 2 and 3)

Study	Results	Company comments
Van Koperen et al 2009 The Dutch multicentre experience of the Endo-SPONGE treatment for anastomotic leakage after colorectal surgery.	• Median time to AL discovery 11 days (3-150). (N=8/16 patients (50%) treated within 6 weeks (early group) and N=8/16 patient treated after 6 weeks (late group) • Overall success healing of AL N=9/16 (56%). • Successful AL closure for 'early' treatment (<6 weeks) n=6/8 (75%). • Successful AL closure for 'late' treatment (>6 weeks) n=3/8 (38%). • No difference between treatment start time and success (P=0.315). • Half patients N=8/16 had a protective stoma created with initial surgery. A further 1 was diverted after AL diagnosis. • Stoma reversed for N=5/9 patents (56%) • Non closure, n=1 complicated by bleeding abscess, n=1 treatment stopped due to pain, n=1 nearly complete dehiscent anastomosis, treatment stopped due to insufficiency of progress, n=2 Recurrent abscesses. • Median 13 sponge changes (8-17) for a median treatment duration of 40 days (28-90) • N=0/16 patient developed sepsis. • Additional surgery was required for N=2/16 patients. **Table 2** Results of the use of the endo-sponge Variable — $n = 16$ Start amount sponges, median (range) — 1 (1–3) Time between surgery and start sponge treatment (days), median (range) — 41 (13-1, 602) ≤6 weeks ($n = 8$, days) — 24 (13–39) >6 weeks ($n = 8$, days) — 74 (43–1,602) Time until closure (days), median (range) — 40 (28–90) Number of sponge exchanges, median (range) — 13 (8–17) Closure of abcsess cavity, n (%) — 9 (56%)	

Table 4 Results of all relevant studies (from tables 1, 2 and 3)

Study	Results	Company comments
Weidenhagen, et al 2008. Endoscopic vacuum-assisted closure of anastomotic leakage following anterior resection of the rectum: a new method	• N=34 patients were included, N=29 were per protocol. • N=21/29 patients had a protective stoma crated with initial surgery, a further 3 stoma were created after AL diagnosis. • The mead abscess size was 7.4±5.1 cm • AL was diagnosis on average 8.2±3.6 days following surgery. • N=28/34 (62.3%) leaks healed overall • N=22/25 of protecting stomas closed during study in 168.9 ± 81.7 days (range 9-321 days). • Duration of endovac therapy 34.4 ± 19.4 days (range 4–79 days). • Number of endoscopic sessions 11.4 ± 6.3 (range 1–27). • Duration of postoperative stay 10-69 days mean 30.5 ± 1 2.8. • In 25 of 29 patients therapy was continued as an ambulatory treatment. • For those patient staying hospital (N=4) median length of stay was 8 days (10-69) • None of the patients reported increase in pain and as reported by the patients, odour due to abscess was significantly better in 24 hours. • Additional surgery was required in N=5/34 patients • Overall N=3 complication were reported N=2 ischemic necrosis, N=1 rectovaginal fistula. • 30 day mortality N=1/34 (this patient fell out of bed and acquired an cranial injury)	

5 Details of relevant studies

Please give details of all relevant studies (all studies in table 4). Copy and paste a new table into the document for each study. Please use 1 table per study.

Arezzo et al 2015 **Long term efficiency of endoscopic vacuum therapy for the treatment of colorectal anastomotic leaks**	
How are the findings relevant to the decision problem?	Paper demonstrates that treatment of colorectal anastomotic leaks with Endo-SPONGE is successful (79%) and can be used in the outpatient setting, providing potential cost savings in n=14 patients.
Does this evidence support any of the claimed benefits for the technology? If so, which?	• Demonstrates Endo-SPONGE is a safe and highly efficient approach to treat colorectal anastomotic leaks (79% success rate and 0/14 complications, 0/14 30 day mortality). • Endo-SPONGE short treatment period compared healing was median 40.5 days (range 8–114). • Demonstrates use of Endo-SPONGE in outpatient setting rather than inpatient for n=14, chronic patient treated as outpatient initially white acute were treated as in patient for only 1 week, then moved to outpatient. – supports change from secondary to community care. • Reduced length of stay – patients treated as outpatients for all chronic leaks and as outpatient for acute after 1 week. • Less staff requirements – insertion of each sponge requires only 1 doctor and 1 nurse. • Demonstrates low level of surgical intervention required – 3/14 (21.5%). • Demonstrates successful treatment irrespective of neoadjuvant therapy (5/7, 71% success with NAR 6/7, 86% success without NAR) p=1.000. •
Will any information from this study be used in the economic model?	• Success rate 79%. • Median number of 12.5 sessions (range 4–40). • Further surgery was required in 3/14 (21.5%) cases.
What are the limitations of this evidence?	• It was uncontrolled and cannot rule out that some fistula would have closed without Endo-SPONGE treatment. • Long recruitment period (4.5 years). It is possible that the surgical technique improved as the study progressed, which could have potentially affected the results • Being a retrospective analysis, subjects were not randomised to closure cohorts or followed prospectively. • Only patients who were treated by Endo-SPONGE have been included. • The number of patients was small and the group was somewhat heterogeneous.
How was the study funded?	No funding declared. No conflicts of interest to declare.

Boschetti et al 2018 **Endo-SPONGE treatment of anastomotic leakage after colorectal surgery: A report of 29 cases compared to the main studies in the literature.**	
How are the findings relevant to the decision problem?	Paper demonstrates that treatment of colorectal anastomotic leaks with Endo-SPONGE is successful (93%) and can be used in the outpatient setting without sedation in N=29 patients. Also provides information on long term continued success.
Does this evidence support any of the claimed benefits for the technology? If so, which?	• Demonstrates Endo-SPONGE is a safe and highly efficient approach to treat colorectal anastomotic leaks (93% success rate, 0/29 complications and 0/29 30 day mortality, high long term success rate 24/29). • Endo-SPONGE can prevent need for long term stoma – as 18/21 85.7% with a protective stoma successfully had stoma reversed, all reversed within 6 months. • Treatment with Endo-SPONGE can reduce need for antibiotics - twelve patients (41%) were on antibiotics before Endo-SPONGE treatment, after a few days (less than 10), the antibiotics were stopped. • Endo-SPONGE changes care from secondary to community care – Endo-SPONGE was inserted as an outpatient without sedation for all without sedation for all patients– reducing staff requirements. • Demonstrates Endo-SPONGE shortened treatment duration compared with conservative treatment - median treatment time 70 days (range 14-196). • Treatment was well tolerated. • Demonstrates low level of surgical intervention required – 1/29 (3.4%). • Reduction in number of patients with permanent stoma, direct impact on improved Quality of life by lack of stoma
Will any information from this study be used in the economic model?	• The cavity was closed in 27/29 (93%) patients. • 85.7% who presented with a stoma experienced a closure of the protective stoma. • Median number of applications 18.6 (range 4-57). • Further surgery required in 1/29 patients
What are the limitations of this evidence?	• It was uncontrolled and cannot rule out that some fistula would have closed without Endo-SPONGE treatment, however the authors report that over half of the patients were referred after failure of common management of AL. • It is a retrospective study without randomisation or controls • Only patients who were treated by Endo-SPONGE have been included. • The number of patients was small and the group was somewhat heterogeneous.
How was the study funded?	No funding or conflicts of interest declared.

Clifford et al 2010 **Early anastomotic complications in colorectal surgery: systematic review of techniques for endoscopic salvage**	
How are the findings relevant to the decision problem?	Paper demonstrates that treatment of colorectal anastomotic leaks with Endo-SPONGE is successful (88%) in n=197 patients.
Does this evidence support any of the claimed benefits for the technology? If so, which?	• Demonstrates Endo-SPONGE is a safe and highly efficient approach to treat colorectal anastomotic leaks in 88.8% (range 66.6–100%) of patients.
Will any information from this study be used in the economic model?	No to prevent repetition of data from individual papers
What are the limitations of this evidence?	No meta-analysis involved, only descriptive systematic review.
How was the study funded?	No funding or conflicts of interest declared.

Huisman et al 2019 **Effectiveness of Endo-SPONGE therapy for the management of presacral abscesses following rectal surgery**	
How are the findings relevant to the decision problem?	Paper demonstrates that treatment of colorectal anastomotic leaks with Endo-SPONGE is successful (85%) in n=20 patients.
Does this evidence support any of the claimed benefits for the technology? If so, which?	• Demonstrates Endo-SPONGE is a safe and highly efficient approach to treat colorectal anastomotic leakage. (N = 17/20 (85%) of patients successful AL healing, N=3/20 complications, 0/20 30 day mortality) • Endo-SPONGE can prevent need for long term stoma/ restore bowel continuity in 14/20 patients (70%), reversal within 7 months in the early treatment group and 10 months in the late treatment group. • Low requirement of extra surgery N=6/20 (30%) • Low level of antibiotic use with Endo-SPONGE (N=1/20 patient was on antibiotics) • Short treatment (Median 9 (2-28) sponge changes, Median treatment duration 25 days (3-115)) • Reduction in number of patients with permanent stoma, direct impact on improved Quality of life by lack of stoma
Will any information from this study be used in the economic model?	• Endo-SPONGE successful (closed leak) in 17/20 (85%) of patients. • 14/20 patients (70%) continuity was restored/stoma reversal. • Further surgery required in 6/20 patients • Median 9 (2-28) sponge changes.
What are the limitations of this evidence?	• It was uncontrolled and cannot rule out that some fistula would have closed without Endo-SPONGE treatment. • It is a retrospective study in which only patients who were treated by Endo-SPONGE have been included.

Huisman et al 2019 **Effectiveness of Endo-SPONGE therapy for the management of presacral abscesses following rectal surgery**	
	• The number of patients was small and the group was somewhat heterogeneous. • LARS data is compared with patients who did not have an AL – difficult to ascertain if LARS score is due to treatment of AL or AL itself.
How was the study funded?	No funding or conflicts of interest declared.

Jimenez-Rodriguez et al **A New Perspective on Vacuum-Assisted Closure for the Treatment of Anastomotic Leak Following Low Anterior Resection for Rectal Cancer, Is It Worthy?**	
How are the findings relevant to the decision problem?	Paper demonstrates that treatment of colorectal anastomotic leaks with Endo-SPONGE is successful (86%) in n=22 patients, with rapid healing in mean 22.3 days.
Does this evidence support any of the claimed benefits for the technology? If so, which?	• Demonstrates Endo-SPONGE is a safe and highly efficient approach to treat colorectal anastomotic leaks (Success rate N=19/22, 86%, Low complication 0/22 during treatment, n=3/22 long term complications, low mortality, 0/22 30 day mortality, n=3/22 long term mortality.). • Demonstrates Endo-SPONGE short treatment duration with rapid healing mean 22.3 days ± 14.7. • Endo-SPONGE changes care from secondary to community care – half of patients were treated as outpatients after initial application. • Reduced length of stay - half of patients were treated as outpatients after initial application. • Endo-SPONGE is well tolerated - all patients experienced discomfort that was well tolerated and that decreased as the size of the sponge introduced decreased. • Endo-SPONGE reduce permanent stoma, N=5/13 stoma reversed • Low complication rate - no patient experienced complications while the treatment was being performed. • Low need for additional surgery – N=2/22 (9%) extra surgery required • Reduction in number of patients with permanent stoma, direct impact on improved Quality of life by lack of stoma
Will any information from this study be used in the economic model?	• Successful colorectal anastomotic leak closure (n=19/22, 86%). • Half of patients were treated as outpatients after initial application. • Extra surgery requirements N=2/22 • Stoma reversal 5/13 • Median 3.1±1.9 sponge changes
What are the limitations of this evidence?	• It was uncontrolled and cannot rule out that some fistula would have closed without Endo-SPONGE treatment. • It is a retrospective study in which only patients who were treated by Endo-SPONGE have been included. • The number of patients was small and the group was somewhat heterogeneous.
How was the study funded?	The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: CIBEREHD was funded

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	by the Instituto de Salud Carlos III, Madrid, Spain. No conflicts of interest declared.

Katz et al 2018 **Different approaches for Endo-SPONGE® insertion to treat rectal anastomotic leaks**	
How are the findings relevant to the decision problem?	Paper demonstrates that treatment of colorectal anastomotic leakage with Endo-SPONGE is successful (100%) in n=6 patients.
Does this evidence support any of the claimed benefits for the technology? If so, which?	• Demonstrates Endo-SPONGE is a safe and highly efficient approach to treat colorectal anastomotic – all (100%) patients fully recovered=0/6 30 day mortality. • Endo-SPONGE can prevent need for long term stoma/ restore bowel continuity, 4/5 (80%) stoma was reversed and 5/6 (83%) regained bowel continuity. • Reduce costs by outpatient treatment – n=3/15 patients treated as out patient • Endo-SPONGE controls sepsis, n=6/6 patients sepsis was controlled. • Reduction in number of patients with permanent stoma, direct impact on improved Quality of life by lack of stoma
Will any information from this study be used in the economic model?	Mean Endo-SPONGE application was 3.6 (range 3-5). Stoma reversed in n=4/5 patients Successful AL healing in n=6/6
What are the limitations of this evidence?	• It was uncontrolled and cannot rule out that some fistula would have closed without Endo-SPONGE treatment. • It is a retrospective study in which only patients who were treated by Endo-SPONGE have been included. • The number of patients was small and the group was somewhat heterogeneous. • Limited details reported.
How was the study funded?	No funding or conflicts of interest declared.

Keskin et al 2015 **Effectiveness of Endoluminal Vacuum-assisted Closure Therapy (Endo-SPONGE) for the Treatment of Pelvic Anastomotic Leakage After Colorectal Surgery**	
How are the findings relevant to the decision problem?	Paper demonstrates that treatment of colorectal anastomotic leakage with Endo-SPONGE is successful (80%) in n=15 patients.
Does this evidence support any of the claimed benefits for the technology? If so, which?	• Demonstrates Endo-SPONGE is a safe and highly efficient approach to treat colorectal anastomotic leakage, n=12/15 (80%) successful AL healing, n=0/15 30 day mortality and 3/15 long term mortality, n=3/15 complications) • Endo-SPONGE can prevent need for long term stoma/ restore bowel continuity, n=10/14 (71%) stoma reversed and n=12/15 (67%) lumen integrity achieved. • Reduction in number of patients with permanent stoma, direct impact on improved Quality of life by lack of stoma • Endo-SPONGE reduced costs by reduced need for surgery n=3/15 required extra surgery.

Keskin et al 2015 **Effectiveness of Endoluminal Vacuum-assisted Closure Therapy (Endo-SPONGE) for the Treatment of Pelvic Anastomotic Leakage After Colorectal Surgery**	
Will any information from this study be used in the economic model?	• Average 2.2 Endo-SPONGE applications (range 1-5). • Low need for extra surgery n=3/15 • Stoma reversal; 10/14 • Median 2.2 (1-5) sponge exchanges needed
What are the limitations of this evidence?	• It was uncontrolled and cannot rule out that some fistula would have closed without Endo-SPONGE treatment. • It is a retrospective study in which only patients who were treated by Endo-SPONGE have been included. • The number of patients was small and the group was somewhat heterogeneous.
How was the study funded?	No funding or conflicts of interest declared.

Kuehn et al 2016 **Endoscopic Vacuum Therapy in Colorectal Surgery**	
How are the findings relevant to the decision problem?	Paper demonstrates that treatment of colorectal anastomotic leakage with Endo-SPONGE is successful (90%) in n=20 patients.
Does this evidence support any of the claimed benefits for the technology? If so, which?	• Demonstrates Endo-SPONGE is a safe and highly efficient approach to treat colorectal anastomotic leakage (n=18/20, 90% successful AL healing, 0/20 30 day mortality rate, 4/20 complications). • Endo-SPONGE can prevent need for long term stoma/ restore bowel continuity, closure of protective enterostomy was possible in 15 of 19 patients (79 %) within 244 days. • Endo-SPONGE supports control of sepsis with sepsis controlled in 27/32 patients. • Reduction in number of patients with permanent stoma, direct impact on improved Quality of life by lack of stoma • Demonstrates Endo-SPONGE short treatment duration, median duration of therapy 23 days (range 2-109). • Reduce length of time with stoma, median time to closure of enterostomy was 244 days (range, 152–488).
Will any information from this study be used in the economic model?	• AL sucessful healing n=18/20 • Stoma reversal n=15/19 • Medain 6 (1-37) sponge exchanges
What are the limitations of this evidence?	• It was uncontrolled and cannot rule out that some fistula would have closed without Endo-SPONGE treatment. • It is a retrospective study in which no randomisation was used • Single centre study • Only patients who were treated by Endo-SPONGE have been included. • Outcome presented by participant group rather than individually
How was the study funded?	No funding or conflicts of interest declared.

Manta et al 2016 **Endoscopic management of patients with post-surgical leaks involving the gastrointestinal tract: a large case series**	
How are the findings relevant to the decision problem?	Paper demonstrates that treatment of colorectal anastomotic leaks with Endo-SPONGE is successful (100%) in n=7 patients without further interventions.
Does this evidence support any of the claimed benefits for the technology? If so, which?	• Demonstrates Endo-SPONGE is a safe and highly efficient approach to treat colorectal anastomotic leaks (100% successful AL healing n=7/7 patients, 0/7 30 day mortality rate) • Demonstrates low level of surgical intervention required – none of the 7 Endo-SPONGE patients required any other intervention, other endoscopic treatments required addition interventions for some patients. • Endo-SPONGE changes care from secondary to community care, initial treatment performed as inpatient then as an outpatient, for n=7/7. • Demonstrates reduced impact of hospital resource as all patients were treated as out patients
Will any information from this study be used in the economic model?	N=7/7 (100%) successful leak closure. N=0/7 extra surgery required
What are the limitations of this evidence?	Retrospective study with focus on all endoscopic events and limited detail provided on each individual endoscopic treatment. Small number of exposure to Endo-SPONGE in study.
How was the study funded?	This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Milito, et al 2017 **Endoluminal Vacuum Therapy as Treatment for Anastomotic Colorectal Leakage**	
How are the findings relevant to the decision problem?	Paper discusses use of Endo-SPONGE reporting on complications
Does this evidence support any of the claimed benefits for the technology? If so, which?	Endo-SPONGE is well tolerated, 5/14 patients reporting mild but manageable pain, with no need to suture the defect
Will any information from this study be used in the economic model?	No
What are the limitations of this evidence?	Details of actual outcome not clear – implies all leaks healed, however this is not actually addressed in the results. Small sample size Only treatment with Endo-SPONGE was included
How was the study funded?	No funding declared. No conflicts of interest.

Mussetto et al 2017 Long term efficacy of vacuum-assisted therapy (Endo-SPONGE) in large anastomotic leakages following anterior rectal resection	
How are the findings relevant to the decision problem?	Paper demonstrates long term success in N=10/10 (100%) patients treated with Endo-SPONGE
Does this evidence support any of the claimed benefits for the technology? If so, which?	• Demonstrates Endo-SPONGE is a safe and highly efficient approach to treat colorectal anastomotic leaks (91% initial successful AL healing n=10/11 patients, 100% long term success N=10/10, 0/7 30 day mortality rate, 2/11 long term mortality rate 2/11 complication rate) • Demonstrates low need for extra surgery with n=1/22 (9%) following Endo-SPONGE treatment
Will any information from this study be used in the economic model?	• Initial success rate n=10/11 (91%) • Median 16 (9-23) sponge changes.
What are the limitations of this evidence?	• It was uncontrolled and cannot rule out that some fistula would have closed without Endo-SPONGE treatment. • It is a retrospective study in which no randomisation was used • Single centre study • Only patients who were treated by Endo-SPONGE have been included. • Outcome presented by participant group rather than individually
How was the study funded?	No funding or conflicts of interest declared.

Nerup et al 2013 Promising results after endoscopic vacuum treatment of anastomotic leakage following resection of rectal cancer with ileostomy	
How are the findings relevant to the decision problem?	Paper demonstrates that treatment of colorectal anastomotic leakage with Endo-SPONGE is successful (100%) in n=13 patients.
Does this evidence support any of the claimed benefits for the technology? If so, which?	• Demonstrates Endo-SPONGE is a safe and highly efficient approach to treat colorectal anastomotic leakage (N=13/13 successful healing of anastomotic cavity, N=1/13 complications, n=0/13 30 day mortality) • Endo-SPONGE can prevent need for long term stoma/ restore bowel continuity, N=12/13 (92%) stoma closure rate of the entire study group. • Endo-SPONGE changes care from secondary to community care – some continued treatment in an outpatient setting. • Endo-SPONGE has low need for extra surgery, N=1/13. • Endo-SPONGE provides short treatment duration 37 days (18-65)
Will any information from this study be used in the economic model?	• N=13/13 successful healing of anastomotic cavity. • N=12/13 (92%) stoma closure rate of the entire study group. • Median length of stay in hospital 25 days (7-39). • Median number of treatments 8 (1-18). • Need for extra surgery N=1/13

Nerup et al 2013 Promising results after endoscopic vacuum treatment of anastomotic leakage following resection of rectal cancer with ileostomy	
What are the limitations of this evidence?	• It was uncontrolled and cannot rule out that some fistula would have closed without Endo-SPONGE treatment. • It is a retrospective study in which only patients who were treated by Endo-SPONGE have been included. • Small sample size.
How was the study funded?	No funding or conflicts of interest declared

Popivanov et al 2019 Endoluminal negative pressure therapy in colorectal anastomotic leaks	
How are the findings relevant to the decision problem?	A systematic review of relevant papers using Endo-SPONGE for treatment of colorectal anastomotic leak demonstrating overall success of 85.4% of leak closure and 72.6% stoma closure rate in 295 patients.
Does this evidence support any of the claimed benefits for the technology? If so, which?	• Demonstrates Endo-SPONGE is a safe and highly efficient approach to treat colorectal anastomotic leak, success rate was 85.4% (80%–91%). • Endo-SPONGE can prevent need for long term stoma/ restore bowel Ileostomy closure was achieved in 72.6%. • Low complication rate. Complications were observed in 19% (13%–25%). •
Will any information from this study be used in the economic model?	• No to prevent using data from original sources more than once
What are the limitations of this evidence?	The limitations are related to the small sample size, the retrospective nature of most of the studies and the lack of large comparative series.
How was the study funded?	No funding or conflicts of interest declared.

Riss et al 209 Endo-SPONGE assisted treatment of anastomotic leakage following colorectal surgery	
How are the findings relevant to the decision problem?	Paper demonstrates that initial treatment of colorectal anastomotic leakage and rectal stump insufficiently with Endo-SPONGE is successful (83%) in n=6 patients.
Does this evidence support any of the claimed benefits for the technology? If so, which?	• Demonstrates Endo-SPONGE is a safe and highly efficient approach to treat colorectal anastomotic leakage (N=5/6 (83.3%) healed for anastomotic leak after rectal resection (n=1/6 required surgery), Complication rate n=6/23 (30%), 30 day mortality n=1/9 (heart attack). • Treatment was well tolerated, patients satisfaction VAS 0 = best, 10 = worst, median = 3 (range 0-9). Alteration in daily life, median = 5 (range 1-9). Pain, median = 3 (range 0-6) • Low complication rate, no complication's observed while using Endo-SPONGE. • Low need for extra surgery n=3/9 (33%) •
Will any information from this study be used in the economic model?	• N=5/6 (83.3%) healed for anastomotic leak after rectal resection. • N=3/6 required surgery. • The median duration of each Endo-SPONGE replacement was 15 min (range: 5– 65).
What are the limitations of this evidence?	• It was uncontrolled and cannot rule out that some fistula would have closed without Endo-SPONGE treatment. • It is a retrospective study in which only patients who were treated by Endo-SPONGE have been included. • Small sample size. • Study was not solely focussed on anastomotic leaks.
How was the study funded?	No funding or conflicts of interest declared.

Riss et al 2010 Recurrent abscess after primary successful Endo-SPONGE treatment of anastomotic leakage following rectal surgery	
How are the findings relevant to the decision problem?	Paper demonstrates that initial treatment of colorectal anastomotic leakage with Endo-SPONGE is successful (87%) in n=23 patients. Long term follow up of n=20 successful treatments demonstrated 75% long term success.
Does this evidence support any of the claimed benefits for the technology? If so, which?	• Demonstrates Endo-SPONGE is a safe and highly efficient approach to treat colorectal anastomotic leakage, (n=20/23 Endo-SPONGE treatments initially successful (87%) and n=5/20 (25%) developed recurrent symptomatic abscess, long term mortality n=4/23, 30 day mortality rate n=0/23) • Demonstrates Endo-SPONGE reduces permanent stoma, Reversal rate N=13/17 (76.5%) • Short treatment duration median 21 days (14-56) • Demonstrates Endo-SPONGE has low need for further surgery N=3/20 additional surgery
Will any information from this study be used in the economic model?	• N=20/23 Endo-SPONGE treatments initially successful (87%). • Stoma reversal N=13/17 (76.5%) • Extra surgery required N=13/20
What are the limitations of this evidence?	• It was uncontrolled and cannot rule out that some fistula would have closed without Endo-SPONGE treatment. • It is a retrospective study in which only patients who were treated by Endo-SPONGE have been included. • Small sample size.
How was the study funded?	No funding or conflicts of interest declared.

Rottoli et al 2018 Endoluminal vacuum-assisted therapy as treatment for anastomotic leak after ileal pouch-anal anastomosis: a pilot study	
How are the findings relevant to the decision problem?	Paper demonstrates that initial treatment of colorectal anastomotic leakage with Endo-SPONGE is successful (100%) in n=8 patients.
Does this evidence support any of the claimed benefits for the technology? If so, which?	• Demonstrates Endo-SPONGE is a safe and highly efficient approach to treat colorectal anastomotic leakage (100%), at a median follow-up time of 11.6 (6–18) months after confirmation of the healing of the anastomotic leak, no recurrence was documented. • Demonstrates Endo-SPONGE short treatment duration, treatment lasted for a median of 12 (3–32) days. • Reduced length of stay, the median length of hospital stay after the first application of the treatment was 15.5 (6–48) days. Overall, the median length of hospital stay (including the postoperative stay from the pouch surgery in seven cases and the closure of ileostomy in one case) was 32 (16–72) days. • Endo-SPONGE can prevent need for long term stoma/ restore bowel continuity. All patients but one (n=7/8, 87.5%) had their ileostomy reversed at a median of 2.5 (1–6) months from the endoscopic confirmation of healing. • Treatment was well tolerated, No patients reported incontinence of faeces or gas. • Demonstrates low need for additional surgery n=1/8 required surgery following Endo-SPONGE treatment
Will any information from this study be used in the economic model?	• The median length of hospital stay after the first application of the treatment was 15.5 (6–48) days. • N=7/8 (87.5%) had their ileostomy reversed at a median of 2.5 (1–6) months from the endoscopic confirmation of healing. • Extra surgery n=1/8
What are the limitations of this evidence?	The principal limitation is the small number of patients.
How was the study funded?	No funding or conflicts of interest declared.

Shalby et al 2019 Systematic review of endoluminal vacuum-assisted therapy as salvage treatment for rectal anastomotic leakage	
How are the findings relevant to the decision problem?	A systematic review of relevant papers using Endo-SPONGE for treatment of colorectal anastomotic leak, demonstrating overall success of 83% of leak closure and 76% stoma closure rate in 276 patients
Does this evidence support any of the claimed benefits for the technology? If so, which?	• Demonstrates Endo-SPONGE is a safe and highly efficient approach to treat colorectal anastomotic leaks, N=228/276 (82.6%) patients healed with endoscopic vacuum therapy. Random-effects meta-analysis showed that the weighted mean success rate of EVT was 85·3 (95 % CI 80·1 to 90·5) % (I^2 =39·7 %) P=0.047. Compared with the current literature, which reports a stoma reversal rate of 30–40 % for clinical leakage, the weighted mean rate of stoma reversal across the studies was 75·9 %. • Endo-SPONGE can prevent need for long term stoma/ restore bowel continuity. N=107/141 underwent reversal of stoma following successful treatment. Random-effects meta-analysis showed the weighted mean rate of stoma reversal across the studies to be 75·9 (95 % CI 64·6 to 87·2) % (I^2 =72·7 %) P<0.001. • EVT has a good safety profile with a mean complication rate of approximately 14 %. Stenosis is the most common complication, and may be caused by anastomotic leakage rather than by EVT.
• Will any information from this study be used in the economic model?	• No to prevent duplication of results from primary sources
What are the limitations of this evidence?	This review has a number of limitations related to the available literature. These include small sample size. The design of most studies was retrospective. Despite the moderate statistical heterogeneity among studies, clinical heterogeneity was significant, including methods, indications and timing. It is therefore not possible to compare these studies on all endpoints. Long-term oncological and functional outcomes are awaited.
How was the study funded?	No funding or conflicts of interest declared

Srinivasamurthy et al 2013 An initial experience using transanal vacuum therapy in pelvic anastomotic leakage	
How are the findings relevant to the decision problem?	Paper demonstrates that initial treatment of colorectal anastomotic leakage with Endo-SPONGE is successful (75%) in n=8 patients with 62.5% stoma reversal.
Does this evidence support any of the claimed benefits for the technology? If so, which?	• Demonstrates Endo-SPONGE is a safe and highly efficient approach to treat colorectal anastomotic leakage. Complete closure N=6/8 (75%), low complication n=1/8 misplaced sponge, n=0/8 30 day mortality. • Endo-SPONGE can prevent need for long term stoma/ restore bowel continuity. Ileostomies reversed and "good function" N=5/8 (N=5 started Endo-SPONGE < 6 weeks, n=4/5 (80%) achieved bowel restoration with good results, N=3 started Endo-SPONGE treatment > 6 weeks, n=1/3 (33%) achieved bowel restoration with good results) • Treatment was well tolerated, n=1 patient complained of discomfort, but the device remained in situ. • Demonstrates low need for extra surgery N=2/8
Will any information from this study be used in the economic model?	• Complete closure or reduction in size of abscess N=6/8. • Ileostomies reversed and "good function" N=5/8. • Median number of sponge applications was 4 (range 1–7), over a median treatment period of 26 days (range 7–49 days). • Extra surgery required for N=2/8
What are the limitations of this evidence?	• It was uncontrolled and cannot rule out that some fistula would have closed without Endo-SPONGE treatment. • It is a retrospective study in which only patients who were treated by Endo-SPONGE have been included. • Small sample size.
How was the study funded?	No funding or conflicts of interest declared

Strangio et al 2015 Endo-SPONGE therapy for management of anastomotic leakages after colorectal surgery: A case series and review of literature	
How are the findings relevant to the decision problem?	Paper demonstrates that initial treatment of colorectal anastomotic with Endo-SPONGE is successful (88%) in n=25 patients.
Does this evidence support any of the claimed benefits for the technology? If so, which?	• Demonstrates Endo-SPONGE is a safe and highly efficient approach to treat colorectal anastomotic leakage, N= 22/25 (88%) patient fully healed anastomotic leakage with sole use of Endo-SPONGE. No abscess recurrence in all 22 healed patients. N = 0/25 30 day mortality rate, and long term mortality rate of 3/12. • Low complication rate n=3/25 (12%) developed complications • Demonstrate Endo-SPONGE short treatment duration Treatment duration of 4 weeks (range 1–32). • Treatment was well tolerated, all patients well tolerated Endo-SPONGE permanence during the treatment interval. • Demonstrates low need for extra surgery following Endo-SPONGE (n=2/25)
Will any information from this study be used in the economic model?	• N= 22/25 (88%) patient fully healed anastomotic leakage with sole use of Endo-SPONGE. • The median number of applications per patient was 9 (1–39 applications). • Extra surgery rate of 2/25 (8%)
What are the limitations of this evidence?	Lack of detailed background information of patients in case series available in tabulated form. Mixed study combining literature review with primary data.
How was the study funded?	No funding or conflicts of interest declared.

Van Koperen et al 2009 The Dutch multicentre experience of the Endo-SPONGE treatment for anastomotic leakage after colorectal surgery	
How are the findings relevant to the decision problem?	Paper demonstrates that initial treatment of colorectal anastomotic leakage with Endo-SPONGE is successful (56%) in n=16 patients.
Does this evidence support any of the claimed benefits for the technology? If so, which?	• Demonstrates Endo-SPONGE is a safe and highly efficient approach to treat colorectal anastomotic leakage. Overall leak closure, N=9/16 (56%), leak closure when treatment start <6 weeks n=6/8 (75%) and when treatment start >6 weeks n=3/8 (38%) P=0.315 between treatment start times and success. Low complications n=4/16, 30 day mortality rate of 0/16. • Endo-SPONGE can prevent need for long term stoma/ restore bowel continuity, stoma closure in 5/9 patients (56%). • Demonstrate Endo-SPONGE short treatment duration, median time to closure 40 days (28-90). • Demonstrates low need for extra surgery n=2/16
Will any information from this study be used in the economic model?	• Overall success rate N=9/16 (56%). • Stoma closure in 5/9 patients (56%). • Time to closure 40 days (28-90). • Number of sponge exchanges 13 (8-17). • Need for extra surgery n=2/16
What are the limitations of this evidence?	• It was uncontrolled and cannot rule out that some fistula would have closed without Endo-SPONGE treatment. • Only patients who were treated by Endo-SPONGE have been included. • Being a prospective analysis, subjects were not randomized to closure cohorts. Nevertheless the baseline characteristics of the patients are displayed and no difference existed in respect to indication for surgery, type of surgery • Small sample size.
How was the study funded?	No funding or conflicts of interest declared

Weidenhagen et al 2008 Endoscopic vacuum-assisted closure of anastomotic leakage following anterior resection of the rectum: a new method.	
How are the findings relevant to the decision problem?	Paper demonstrates that initial treatment of colorectal anastomotic leakage with Endo-SPONGE is successful (96.5%) in n=29 patients.
Does this evidence support any of the claimed benefits for the technology? If so, which?	• Demonstrates Endo-SPONGE is a safe and highly efficient approach to treat colorectal anastomotic leakage, N=28/29 leaks healed, low complications n=3/34, 30 day mortality rate 1.34 (fell out of bed and cranial injury) • Endo-SPONGE can prevent need for long term stoma/ restore bowel continuity, n=22/25 of protecting stomas closed. • Reduce length of time with stoma, stoma reversed in a mean of 168.9 ± 81.7 days (range 9-321 days). • Demonstrates Endo-SPONGE short treatment duration, duration of endovac therapy 34.4 ± 19.4 days (range 4–79 days). • Endo-SPONGE changes care from secondary to community care n=25/29 (86.2%) patients therapy was continued as an ambulatory treatment. • Treatment was well tolerated. • None of the patients reported increase in pain and as reported by the patients, odour due to abscess was significantly better in 24 hours. • Demonstrates low need for extra surgery.
Will any information from this study be used in the economic model?	• n=22/25 of protecting stomas closed during study in 168.9 ± 81.7 days (range 9-321 days). • Duration of Endovac therapy 34.4 ± 19.4 days (range 4–79 days). • Number of endoscopic sessions 11.4 ± 6.3 (range 1–27). • Duration of postoperative stay 10-69 days mean 30.5 ± 12.8. • In 25 of 29 patients therapy was continued as an ambulatory treatment. • Need for extra surgery 5/34
What are the limitations of this evidence?	• It was uncontrolled and cannot rule out that some fistula would have closed without Endo-SPONGE treatment. • It is a retrospective study in which only patients who were treated by Endo-SPONGE have been included. • Small sample size.
How was the study funded?	No funding or conflicts of interest declared.

6 Adverse events

Describe any adverse events and outcomes associated with the technology in national regulatory databases such as those maintained by the MHRA and FDA (Maude). Please provide links and references.

No manufacturer field safety notices or medical device alerts for this technology have been issued.

No recall/FSCA related to Endo-SPONGE has been registered.

No CAPA's related to Endo-SPONGE has been registered.

Complaints of Endo-SPONGE are very low, between 0% and 0.069%.

There was one vigilance case which was reported to NCA. **400424817**: Complaint description: Sponge clogged, does not work. The problem according to the costumer is that there is no suction out despite applied vacuum. Three changes in one week instead of one. No used sample is available. The lot number is not known according to the received information. It could be 218343. The involved batch number is not known (possible batch is 218343). There are no previous complaints of this code-batch. We have checked the batch manufacturing record of this possible code-batch and no deviations have been found. Regarding the time of the sponge in the patient, we have received the information that the sponge that was clogged/blocked was 2-3 days in the patient meaning that follows instructions for use. According to the Instructions for Use of the product, the maximum use of Endo-SPONGE is 72 hours. Final conclusion: no remedial/corrective/preventive and Field Safety Corrective Actions are applicable at this time.

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Table 6.1

Endo-SPONGE	Quantity in Units								
	2012	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**	**Jan-Sept 2019**	**Total**
Sales (Units)	17,281	18,403	21,244	18,117	20,222	23,075	24,134	18,728	161,204
Complaints (total)	0	0	0	2	0	5	4	13	24
Complaint rate (total) [%]	0%	0%	0%	0.011%	0%	0.021%	0.016%	0.069%	0.014%
Complaints (confirmed)	0	0	0	0	0	4	3	7*	14
Complaint rate (confirmed) [%]	0	0	0	0	0	80%	75%	53%	58%
Reported to NCA	0	0	0	0	0	0	0	1	1
Complaints (total)	0	0	0	2	0	5	4	13	24
Reported to NCA	0	0	0	0	0	0	0	1	1
Reported to EU NCA	0	0	0	0	0	0	0	1	1
Reported to non EU nor FDA NCA	0	0	0	0	0	0	0	0	0
Reported to FDA	0	0	0	0	0	0	0	0	0

*(+4 still under analysis)

Describe any adverse events and outcomes associated with the technology in the clinical evidence.

Study	Adverse Events
Arezzo et al 2010	Not discussed in paper
Arezzo et al 2015	0/14 patients experienced complications/adverse events
Borstlap et al 2018	Not discussed in paper
Boschetti et al 2018	0/29 complications/ adverse events
Chopra et al 2009	Not discussed in paper
D'Hondt et al 2010	Not discussed in paper
Gardenbroek et al 2014	Not discussed in paper
Heeney et al 2010	Not discussed in paper
Hoogenboom et al 2010	Not discussed in paper
Huisman et al 2019	3/20 chronic sinus
Jimenez-Rodriguez et al 2018	22/22 patients experienced discomfort, well tolerated 1/22 anastomotic stenosis 1/22 chronic fistula 1/22 osteomyelitis
Katz et al 2018	Not discussed in paper
Keskin et al, 2015	2/15 sepsis 1/15 bleeding
Knuth et al 2016	0/1 complication/ adverse events
Kuehn et al, 2016	3/20 stenosis 1/20 bleeding
Manta et al 2016	Not discussed in paper
Martinotti et al 2014	0/4 complication/ adverse events
Milito et al 2017	5/14 mild pain
Mussettos et al 2017	2/11 anastomotic stricture
Nerup et al, 2013	1/13 stenosis
Riss et al, 2009	0/6 complications/ adverse events
Riss et al, 2010	1/23 stenosis 5/23 recurrent abscess
Rottoli et al 2018	Not discussed in paper
Srinivasamurthy et al,	1/8 pain, 1/8 inadvertent placement of Endo-SPONGE 1/8 fistula
Strangio et al, 2015	1/25 urethirc fistula 1/25 ileal fistula 1/25 para-rectal abscess
Terzian et al 2016	Not discussed in paper
Van Koperen et al, 2009	1/16 bleeding 500 cc 1/16 pain stopped therapy 1/16 stopped due to near complete dehiscent anastomosis 1/16 recurrent abscess.
Verlaan et al 2011	Not discussed in paper
Weidenhagen et al, 2008	0/34 pain, 0/34 major bleeding. Minor bleeding mentioned without details of frequency 2/34 ischemic necrosis 1/34 rectovaginal fistula
Wood et al 2015	N=1 case of fungal endophthalmitis

Bleeding was reported in 4 different articles, mostly described as mild and to stop spontaneously, and forcing treatment discontinuation (n=2), and n=1 large volume bleeding. The event is listed in the IFU of Endo-SPONGE.

Fistula formation was reported in 4 different articles is not clear whether fistula was caused by Endo-SPONGE or by the nature of the anastomotic leak, however fistula formation is listed in the IFU of Endo-SPONGE.

Anastomotic stenosis was reported in 4 different articles. It has been reported to be one of the main complications in the management of anastomotic leaks, and even linked to anastomotic leakage rather than by EVT (Shalaby et al. 2019). However, the event is listed in the IFU of Endo-SPONGE.

Pain has been reported in 4 different articles, mostly mild and occasionally severe leading to discontinuation in some cases. The event is listed in the IFU of Endo-SPONGE.

Abscess has been reported in 3 different articles, due to the underlying disease most patients have a localised infection which can lead to abscess.

Misplacement placement of the sponge was reported in single case in a single article

Fungal endophthalmitis was reported in a single case report article (Wood, Wright, and Witherspoon 2015) which is analysed in Section **Error! Reference source not found.**.

Overall, the use of the Endo-SPONGE was reported as a safe technology throughout the Product literature analysis, and the reported adverse events associated to the technology were in general not severe.

7 Evidence synthesis and meta-analysis

Although evidence synthesis and meta-analyses are not necessary for a submission, they are encouraged if data are available to support such an approach.

If an evidence synthesis is not considered appropriate, please instead complete the section on qualitative review.

If a quantitative evidence synthesis is appropriate, describe the methods used. Include a rationale for the studies selected.

Recent systematic reviews with meta-analyses have been performed by Shalaby et al 2019 and by Popinanov et al 2019. Results from these meta analyses shall be discussed here as shall the descriptive quantitative outcomes.

Meta-analysis methods in Shalaby et al 2019:
A meta-analysis of the rates of treatment success, stoma reversal and complications across the studies was conducted using open-source, cross-platform software for advanced meta-analysis, openMeta[Analyst]™ version 12.11.14 (http://www.cebm.brown.edu/openmeta/). Data were pooled and weighted mean rates with 95 % CI calculated. Statistical heterogeneity was determined with Cochrane's Q test and I^2 statistics. Heterogeneity was considered low when I^2 was less than 25 % and high when I^2 was greater than 75 %. If significant statistical heterogeneity was not present a fixed- effect model was used to pool data, whereas in the case of significant statistical heterogeneity (P<0·100) the binary random-effects model was employed for pooling of data. A random-effects meta-regression model was used, weighing the studies by their within-study variance and degree of heterogeneity to determine the predictive factors for failure of EVT in the treatment of anastomotic leakage. Heterogeneity between studies was explored in relation to differences in patient age, sex, creation of a stoma before EVT, radiotherapy, development of complications and duration of treatment. The statistical significance of each examined variable was examined using the slope coefficient (s.e.) and P value.

Meta-analysis Popivanov et al 2019
Data were analysed using OpenMetaAnalyst (https:/ www.cebm.brown.edu/openmeta/). The included variables are presented as median values. Heterogeneity for each analysed variable was explored using tau squared, Cochran's Q and I^2. Heterogeneity was considered significant when the null hypothesis of the Q test was rejected and when the coefficient of inconsistency I^2 was higher than 50%. When heterogeneity was considered low, a binary random-effects model was applied to pool data, whereas if statistically significant heterogeneity was proved when the fixed-effects model was run. In most cases, random-effects models were applied for estimating the weighted mean rates. The results are presented as forest plots.

Meta-analysis has been performed on papers submitted here, following the same technique as Popivanov et al 2019 for success rate, stoma reversal rate and complication rate. From median and range data for days of treatment and number of sessions, the mean and SD were estimated using methods as described by Hozo, Djulbegovic and Hozo 2005 http://bmcmedresmethodol.biomedcentral.com/articles/10.1186/1471-2288-5-13
using the conversion calculator
http://vassarstats.net/median_range.html
Then weighted means analysed using continuous random effects using OpenMetaAnalyst.
Other evidence synthesis has been performed as a quantitative review of available data using all papers submitted in section 4 based on data abstraction with regards to: Number of participants, Frequency of sponge change and in/outpatient use of technology.

Report all relevant results, including diagrams if appropriate.

Shalaby et al 2019:
Anastomosis healing rate, n=228/276 (82.6%). Random-effects meta-analysis showed that the weighted mean success rate of EVT was 85·3 % (95 % CI 80·1 to 90·5) (I^2 =39·7 %).

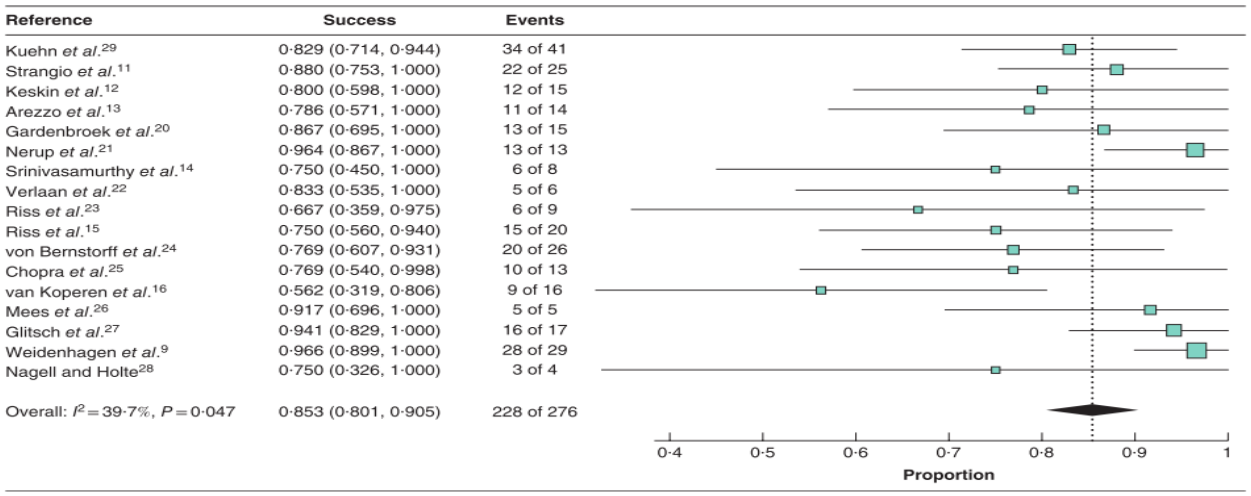


Fig. 3 Forest plot for success rate of endoluminal vacuum-assisted therapy across the studies. A random-effects model was used for meta-analysis. Success rates are shown with 95 per cent confidence intervals

Stoma reversal details. A total of 141 patients had faecal diversion, N=107/141 underwent reversal of stoma following successful treatment. Random-effects meta-analysis showed the weighted mean rate of stoma reversal across the studies to be 75·9% (95 % CI 64·6-87·2) (I^2 =72·7 %).

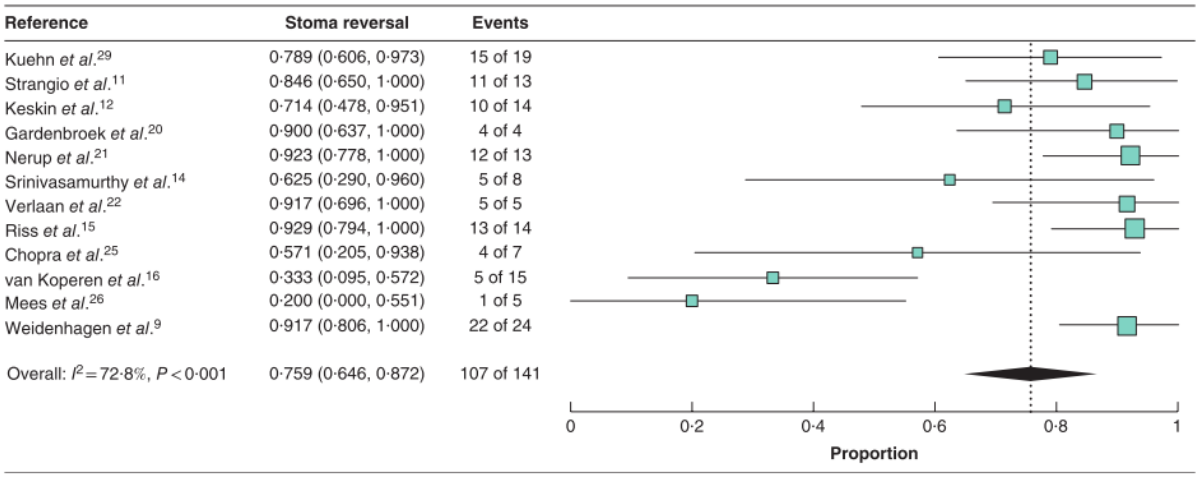


Fig. 4 Forest plot for stoma reversal rate after endoluminal vacuum-assisted therapy across the studies. A random-effects model was used for meta-analysis. Stoma reversal rates are shown with 95 per cent confidence intervals

Complication rate Thirty-eight patients (13·8 %) developed complications after EVT. Random-effects meta-analysis showed that the mean complication rate across the studies was 11·1% (95%CI 6·0 to 16·2) (I^2 =65·1%).

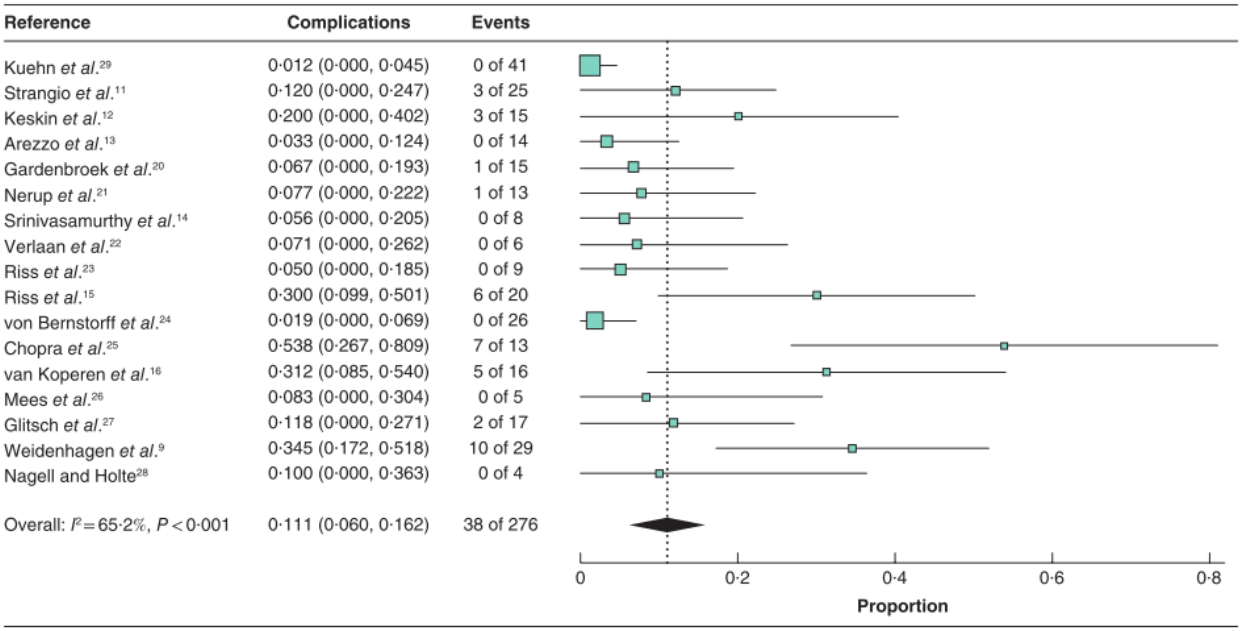


Fig. 5 Forest plot for complication rate of endoluminal vacuum-assisted therapy across the studies. A random-effects model was used for meta-analysis. Complication rates are shown with 95 per cent confidence intervals

Technical details and outcome of EVT treatment in the studies included in Shalaby et al 2019

Study	Using adjunct treatment	Frequency of changing sponge	Median duration of therapy in days (range)	Success of treatment (%)	Complications (%)	Mortality (%)
(Kuehn, Janisch, et al. 2016) 2016	None	Every 3 days	244 (152-488)	34/41 (82.9)	0	0
(Strangio et al. 2015a) 2015	None	Every 2-3 days	34 (1-221)	22/25 (88)	3/25 (12)	0
, (Keskin et al. 2015) 2015	None	Every 3-4 days	NA	12/15 (80)	3/15 (20)	3 (20)
(Arezzo et al. 2015a) 2015	None	2-3 times per week	40.5 (8-114)	11/14 (78.5)	0	0
(Gardenbroek et al. 2015) 2015	Surgical closure of defect	Every 3-4 days	48 (25-103)	13/15 (86.6)	1/15 (6.6)	0
(Nerup et al. 2013) 2013	None	Every 2-3 days	18 (3-40)	13/13 (100)	1/13 (7.6)	0
(Srinivasamurthy et al. 2013b) 2013	None	NA	26 (7-49)	6/8 (75)	0	0
, (Verlaan et al. 2011) 2011	Suturing (1) Endoclip (1)	Every 3-4 days	13.8 (5-28)	5/6 (83.3)	0	0
(Riss, Stift, Meier, et al. 2010) 2010	None	Every 2-3	21	6/9 (66.6)	0	1 (11.1)
(Riss, Stift, Kienbacher, et al. 2010) 2010	Stent - Fibrin glue	Every 2-3 days	21	15/20 (75)	6/20 (30)	5 (25)
, (von Bernstorff et al. 2009) 2009	None	Every 2-4 days	21.5 (4-88)	20/26 (76.9)	0	0
(Chopra, Mrak, and Hunerbein 2009) 2009	Stent (6) Fibrin glue (2)	Every 3-5 days	11 (7-14)	10/13 (76.9)	7/13 (53.8)	0
(van Koperen et al. 2009) 2009	None	Every 3-4 days	40 (28-90)	9/16 (56.2)	5/16 (31.2)	0
(Mees et al. 2008) 2008	None	Every 3 days	27 (18-37)	5/5 (100)	0	0
(Glitsch et al. 2008) 2008	Intramural fibrin glue injection	Every 2days then every 3-4 days	21.4 (4-88)	16/17 (94.1)	2/17 (11.7)	0
(Weidenhagen et al. 2008b) 2008	Intramural fibrin glue injection	Every 2-3 days	34.4 (4-79)	28/29 (96.5)	10/29 (34.4)	0
(Nagell and Holte 2006) 2006	None	Every 2-3 days	51 (43-195)	3/4 (75)	0	1 (25)
Total	------	------	------	228/276 (82.6)	38/276 (13.8)	10/276 (3.6)

Predictors for success of EVT therapy of AL Shalaby et al 2019

Study	Median age in years (range)	Male patients (%)	Creation of stoma before treatment (%) (Both at the original operation or after diagnosing AL)	Preoperative radiation therapy (%)	Median duration of treatment in days (range)	Failure of closure of anastomotic defect (%)
(Kuehn, Janisch, et al. 2016) 2016	70 (29-91)	31/41 (75.6)	19/41 (46.3)	31/41 (75.6)	244 (152-488)	7/41 (16.1)
(Strangio et al. 2015a) 2015	67 (37-89)	18/25 (72)	13/25 (52)	8/25 (32)	34 (1-221)	3/25 (12)
(Keskin et al. 2015) 2015	55 (25-72)	7/15 (46.6)	14/15 (93.3)	6/15 (40)	NA	3/15 (20)
(Arezzo et al. 2015a) 2015	68 (55-85)	7/14 (50)	8/14 (57.1)	7/14 (50)	40.5 (8-114)	3/14 (21.5)
(Gardenbroek et al. 2015) 2015	37 (25-56)	12/15 (80)	4/15 (26.6)	0	48 (25-103)	2/15 (13.4)
(Nerup et al. 2013) 2013	64 (36-71)	11/13 (84.6)	13/13 (100)	6/13 (46.1)	18 (3-40)	0
(Srinivasamurthy et al. 2013b) 2013	66.5 (45-79)	7/8 (87.5)	8 /8(100)	7 /8(87.5)	26 (7-49)	2/8 (25)
(Verlaan et al. 2011) 2011	50.2 (29-68)	5/6 (83.3)	5 /6 (83.3)	1/6 (16.6)	13.8 (5-28)	1/6 (16.7)
(Riss, Stift, Meier, et al. 2010) 2010	63.5 (50-71)	5/9 (55.5)	4/9 (44.4)	4/9 (44.4)	21	3/9 (33.4)
(Riss, Stift, Kienbacher, et al. 2010) 2010	66.3 (54.8-91.2)	13/20 (65)	14/20 (70)	6/20 (30)	21	5/20 (25)
(von Bernstorff et al. 2009) 2009	62.4 (42-84)	21/26 (80.7)	20/26 (76.9)	14/26 (53.8)	21.5 (4-88)	6/26 (23.1)
(Chopra, Mrak, and Hunerbein 2009) 2009	65 (33-83)	NA	7/17 (53.8)	6/17 (46.1)	11 (7-14)	3/17 (23.1)
(van Koperen et al. 2009) 2009	64 (19-78)	9/16 (56.2)	15/16 (93.7)	11/16 (68.7)	40 (28-90)	7/16 (43.8)
(Mees et al. 2008) 2008	46 (33-65)	4/5 (80)	5/5 (100)	0	27 (18-37)	0
(Glitsch et al. 2008) 2008	61.2 (42-84)	14/17 (82.3)	13/17 (76.5)	9/17 (52.9)	21.4 (4-88)	1/17 (5.9)
(Weidenhagen et al. 2008b) 2008	66.7 (42-79)	24/29 (82.7)	24/29 (82.7)	9/29 (31)	34.4 (4-79)	1/29 (3.5)
(Nagell and Holte 2006) 2006	75 (73-78)	NA	4/4 (100)	1/4 (25)	51 (43-195)	1/4 (25)
Total	61.6	188/276	190/276	126/276	------	48/276

Popivanov et al 2019:

Anastomosis healing rate, n=233/281 (82.9%). Random-effects meta-analysis showed that the weighted mean success rate of EVT was 85.4% (95 % CI 80·1 to 90·6) (I^2 =44%).

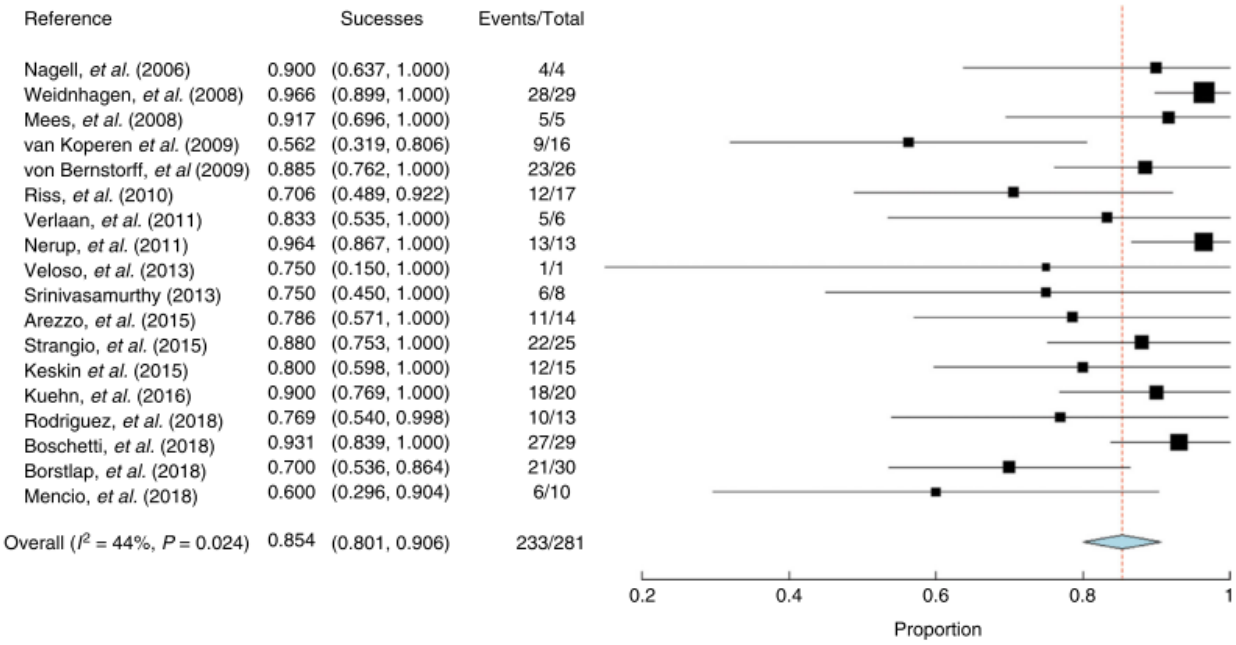


Figure 4 Success rate.

Stoma reversal details. A total of 196 patients had faecal diversion N=142/196 (72.4%) underwent reversal of stoma following successful treatment. Random-effects meta-analysis showed the weighted mean rate of stoma reversal across the studies to be 72·6% (95% CI 61·6 to 83·6) (I^2 =77 %).

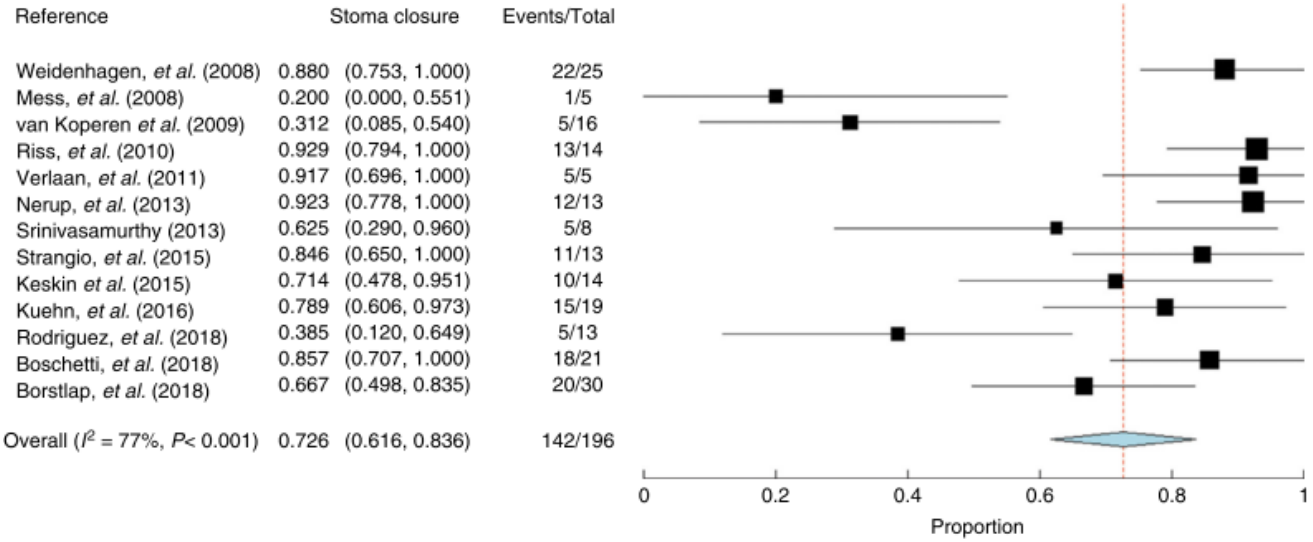


Figure 5 Stoma closure rate.

Complication rate N=61/279 (21.9%) developed complications after EVT. Random-effects meta-analysis showed that the mean complication rate across the studies was 19.9% (95% CI 12.8 to 25.1) (I^2 =49%).

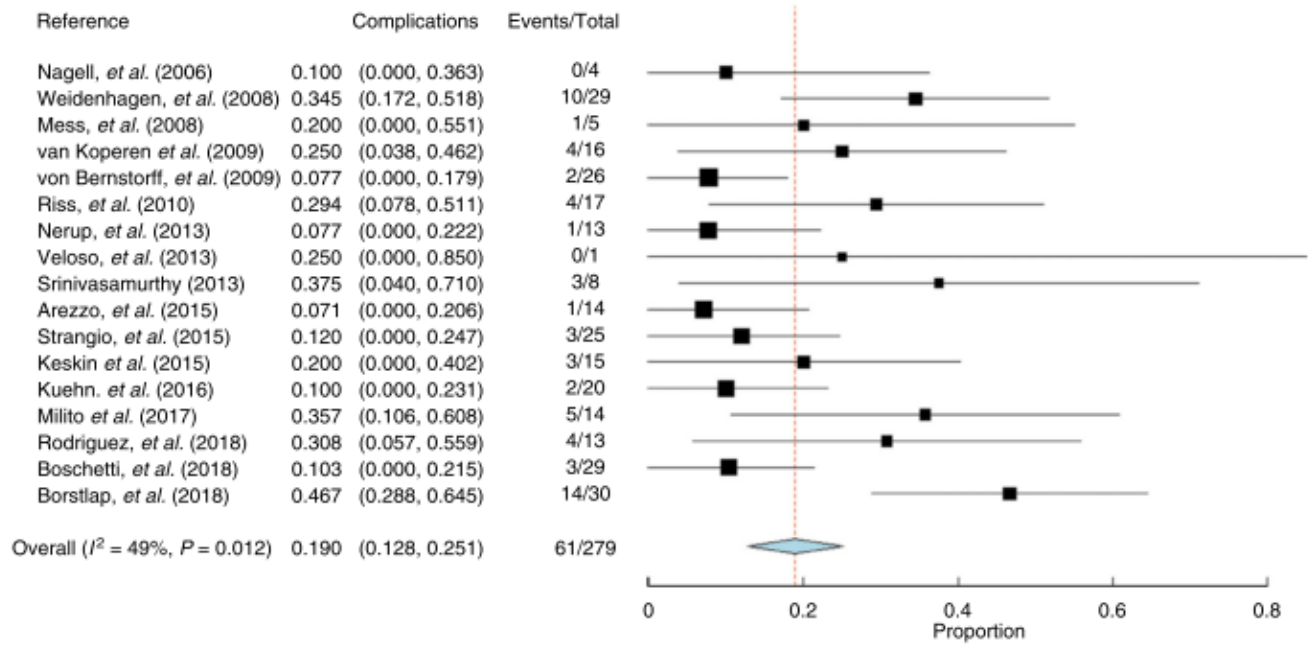


Figure 6 Complications rate.

Table 1 The descriptive analysis of ENPT in insufficiency of low colorectal anastomoses.

			Stoma				Success	
Study	Year	*n*	*n*	%	Days	Sponges, *n*	*n*	%
Nagell *et al.* [29]	2006	4	4	100	51	–	4	100
Weidenhagen *et al.* [30]	2008	29	25	86	34	11	28	96
Mees *et al.* [31]	2008	5	5	100	28	7	5	100
Van Koperen *et al.* [24]	2009	16	16	100	40	13	9	56
von Bernstorff *et al.* [13]	2009	26	18	69	50	10	23	89
Riss *et al.* [11]	2010	17	13	77	21	7	12	71
Verlaan *et al.* [33]	2011	6	5	83	14	3	5	100
Nerup *et al.* [28]	2013	13	13	100	18	8	13	100
Veloso *et al.* [36]	2013	1	0	0	75	34	1	100
Srinivasamurthy *et al.* [26]	2013	8	8	100	21	4	6	75
Arezzo *et al.* [25]	2015	14	8	57	41	13	11	79
Strangio *et al.* [34]	2015	25	13	52	28	9	22	88
Keskin *et al.* [27]	2015	15	–	–	–	2	12	80
Kuehn *et al.* [7]	2016	20	19	95	23	7	18	90
Milito *et al.* [32]	2017	14	14	100	37	(3–14)	–	–
Jimenez-Rodriguez *et al.* [35]	2018	13	13	100	24	3	10	77
Boschetti *et al.* [8]	2018	29	21	72	70	19	27	93
Borstlap *et al.* [3]	2018	30	20	67	127	3.5	21	70
Mencio *et al.* [9]	2018	10	9	90	24	6	6	60
Total†, median (range)	–	295	224/280	84.5	31 (14–127)	7 (2–34)	233/281	85.4

n, patients; days, days of treatment; success, complete closure of the abscess cavity.
†The proportions are based on the random analysis; the continuous variables are presented as median values.

Table 2 Descriptive analysis of the secondary outcome variables.

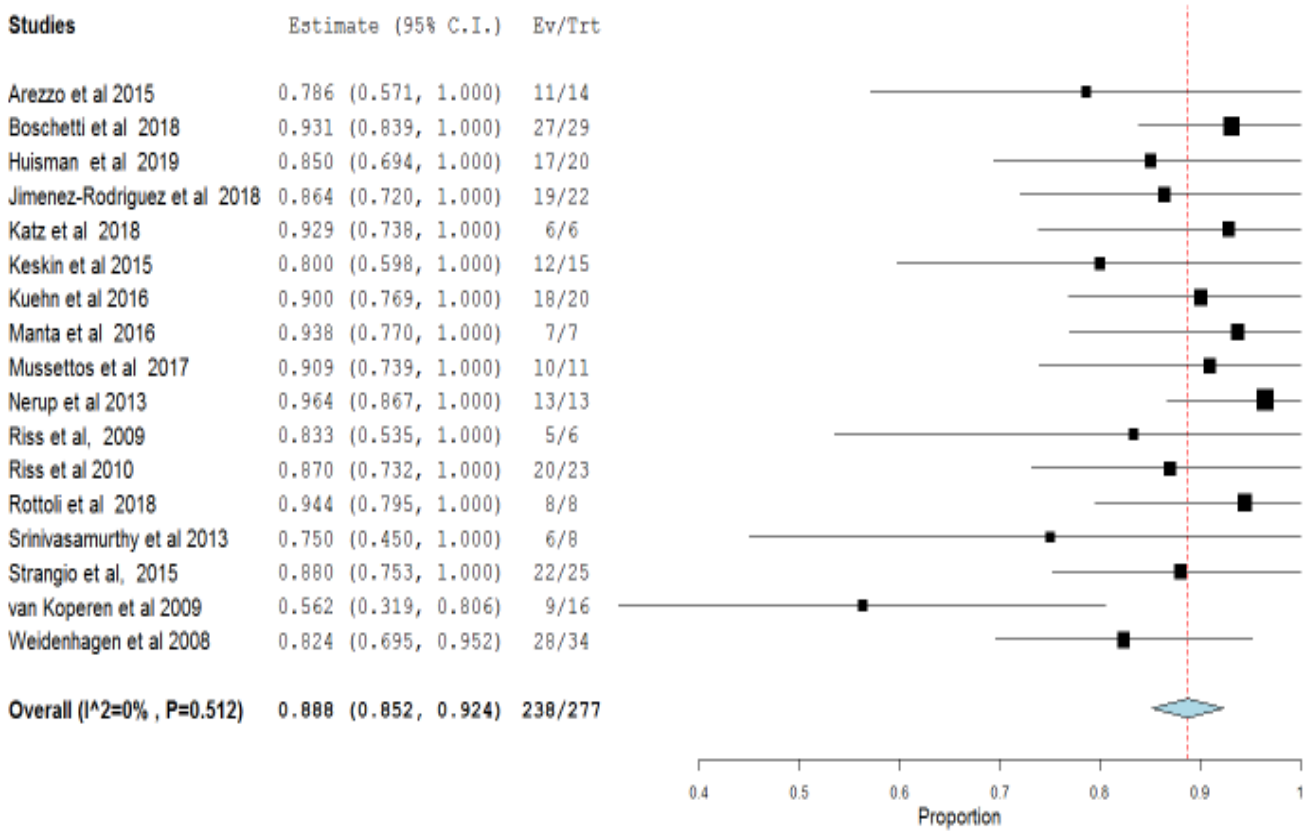
Study	*n*	cm	NR		mmHg	Abscess size (cm)	Stoma closure	
			n	%			*n*	%
Nagell *et al.* [29]	4	–	1	25	125	–	–	–
Weidenhagen *et al.* [30]	29	5.3	9	31	–	–	22/25	88
Mees *et al.* [31]	5	(4–7)	0	0	166	6.5	1/5	20
Van Koperen *et al.* [24]	16	5	11	68	–	–	5/16	31
von Bernstorff *et al.* [13]	26	–	14	54	–	–	–	–
Riss *et al.* [11]	17	–	6	35	–	–	13/14	76
Verlaan *et al.* [33]	6	–	1	17	–	–	5/5	100
Nerup *et al.* [28]	13	9	6	46	–	–	12/13	97
Veloso *et al.* [36]	1	10	1	100	–	6.0	–	–
Srinivasamurthy *et al.* [26]	8	–	6	75	–	–	5/8	62
Arezzo *et al.* [25]	14	–	7	50	(700–200)	5.0	–	–
Strangio *et al.* [34]	25	–	8	32	150	5.6	11/13	85
Keskin *et al.* [27]	15	–	–	–	–	–	10/14	71
Kuehn *et al.* [7]	20	–	15	75	125	–	15/19	79
Milito *et al.* [32]	14	3–7	–	–	–	8.1	–	–
Jimenez-Rodriguez *et al.* [35]	13	4.9	–	–	150	5.9	5/13	38
Boschetti *et al.* [8]	29	6.3	19	66	125	7.0	18/21	86
Borstlap *et al.* [3]	30	–	22	73	–	–	20/30	67
Total†, median (range)	285	5.65 (4.9–10)	126/243	48.6	150 (125–700)	6.0 (5–8.1)	142/196	72.6

NR, neoadjuvant radiotherapy.
†The proportions are based on the random analysis; the continuous variables are presented as median values.

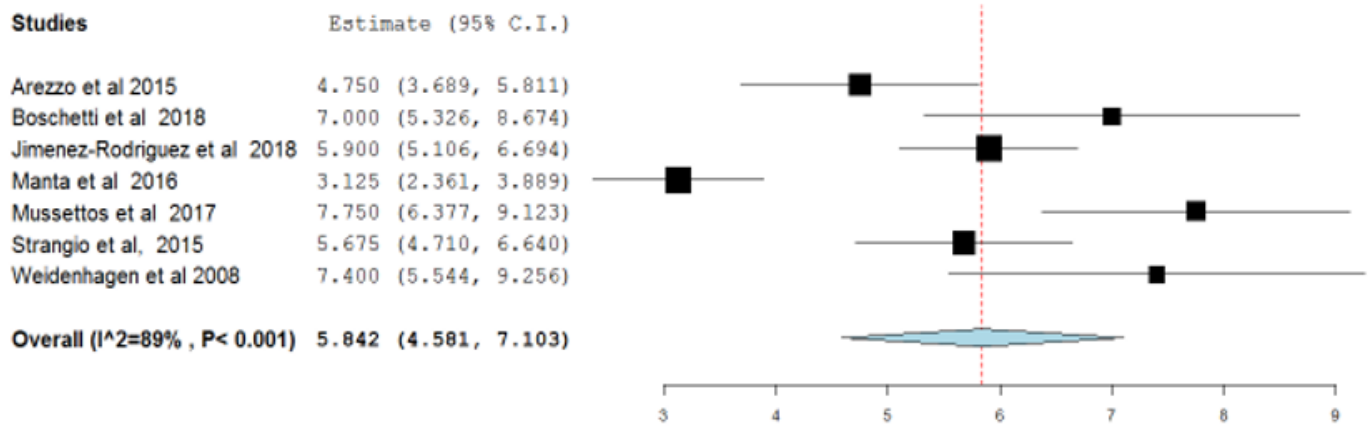
Meta-analysis from systematic search in this document

Any publication which has not used the CE marked Endo-SPONGE device (i.e. investigators have used other negative pressure devices not indicated for treatment of anastomotic leaks) have been excluded from the below analysis.

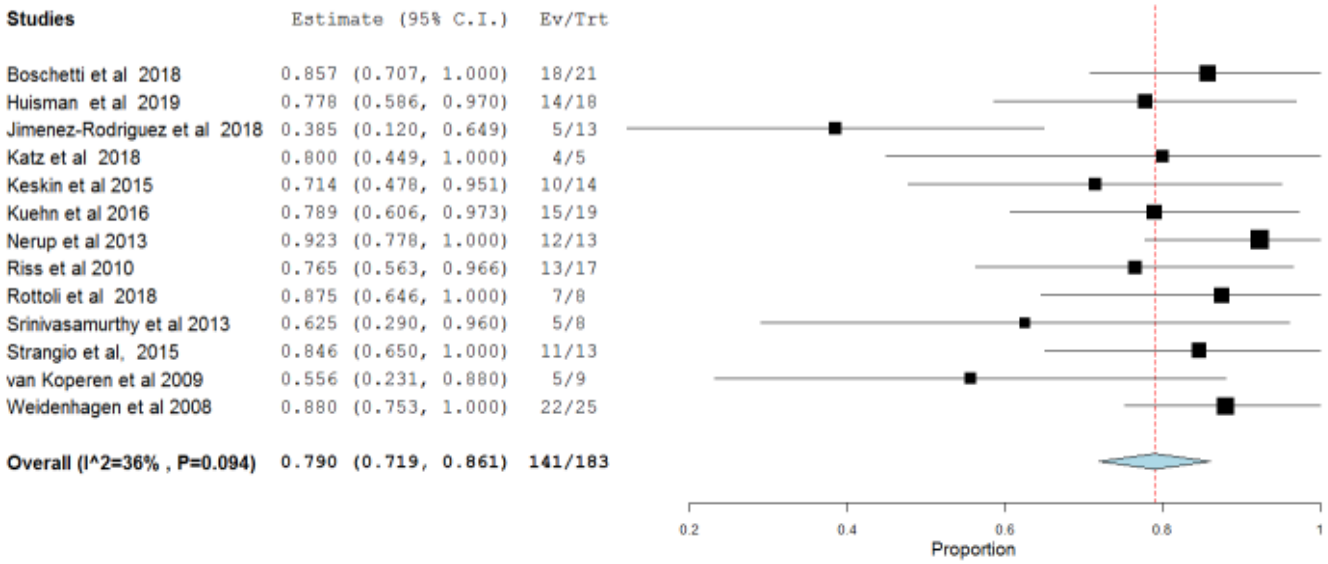
Anastomosis healing rate, n=238/277 (85.9%). Random-effects meta-analysis showed that the weighted mean success rate of Endo-SPONGE was 88.8% (95% CI. 85.2 to 92.4) (I^2 =9%).



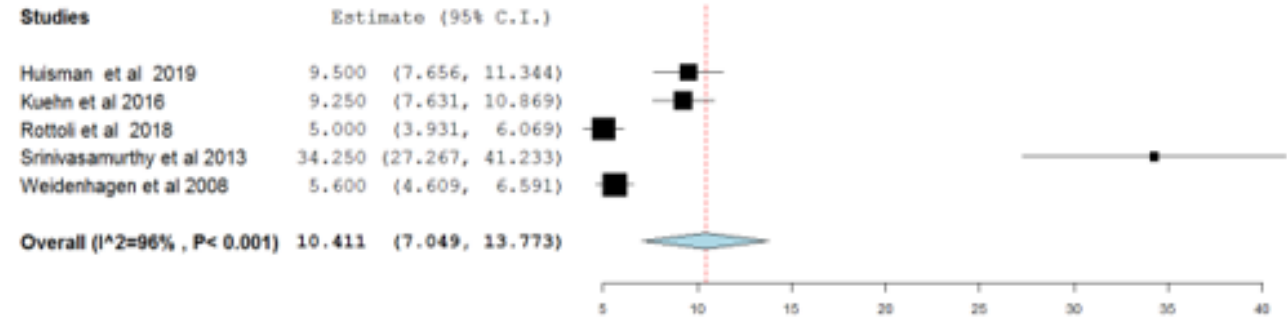
Anastomosis abscess size, Endo-SPONGE was observed being used in leaks with abscess ranging from 1.5cm up to very large abscesses of 20.0 cm. Continuous random effects showed that the weighted mean size of abscesses treated with Endo-SPONGE was 5.82cm (95% CI 4.58 to 7.10 cm) I^2 = 89%.



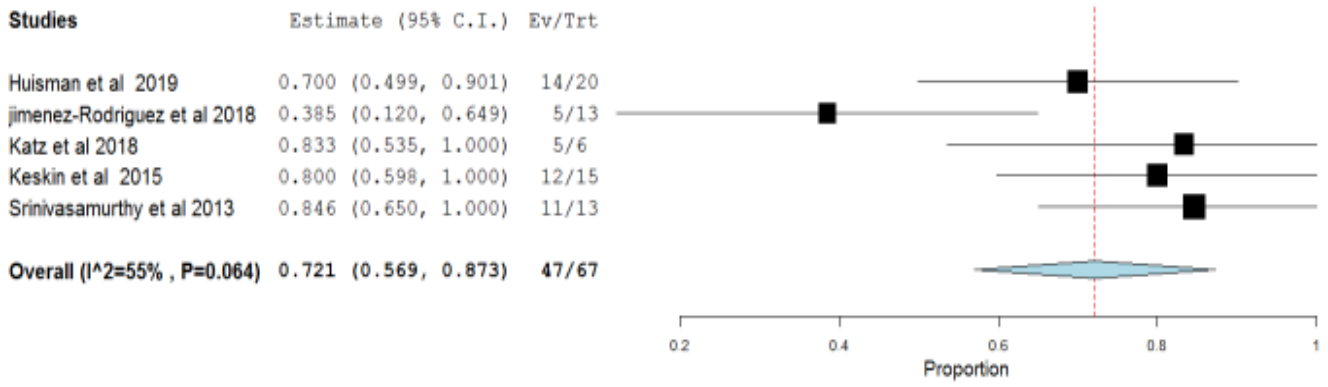
Stoma reversal rate. A total of 183 patients had faecal diversion N=141/183 (77.0%) underwent reversal of stoma following successful treatment. Binary random-effects meta-analysis showed the weighted mean rate of stoma reversal across the studies to be 79.0% (95%CI 71.9 to 86.1) (I^2 =36%).



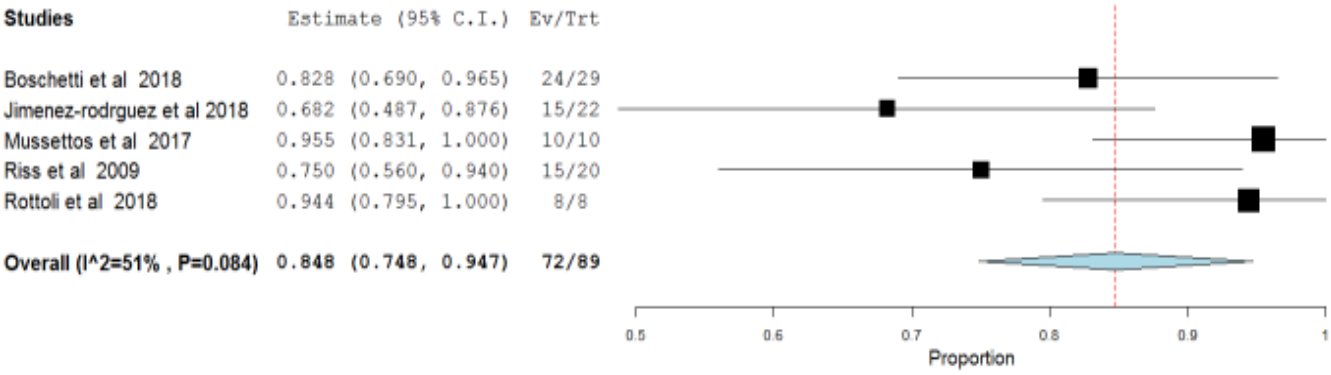
Time to stoma reversal Binary random-effects meta-analysis showed the weighted mean time to stoma reversal was 10.41 months (95%CI 7.05 to 13.77 months) (I^2 =96%).



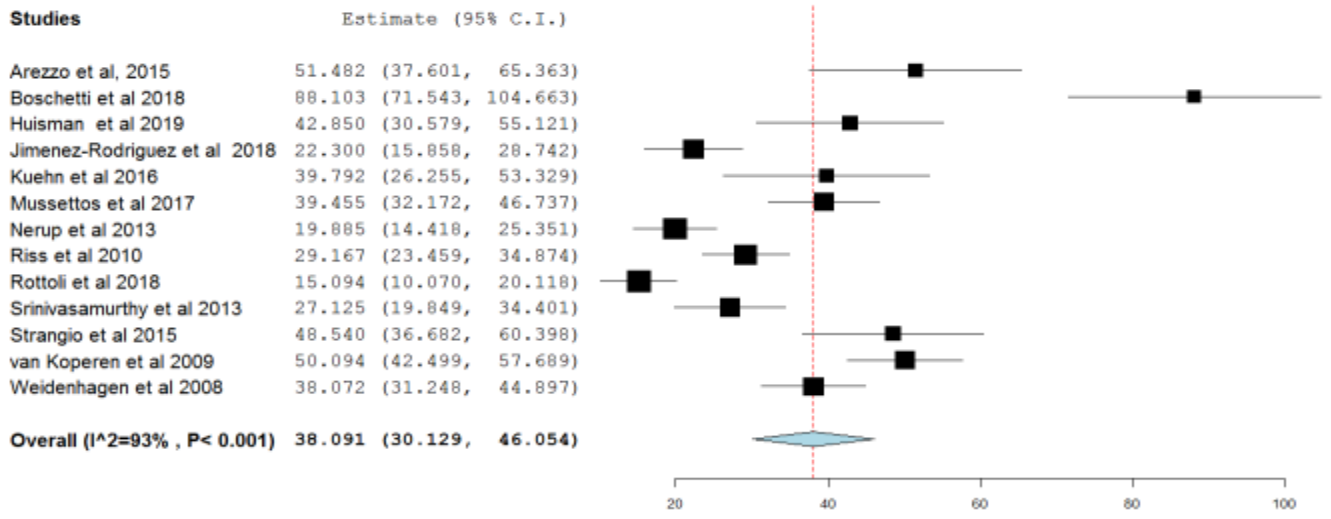
Bowel continuity N=67 patients discussed bowel continuity, successful bowel continuity was achieved in 47/67 (70.1%) patients. Binary random-effects meta-analysis showed that the mean successful bowel continuity rate across the studies was 72.1% (95% CI 56.9 to 87.3) (I^2 =72.1).



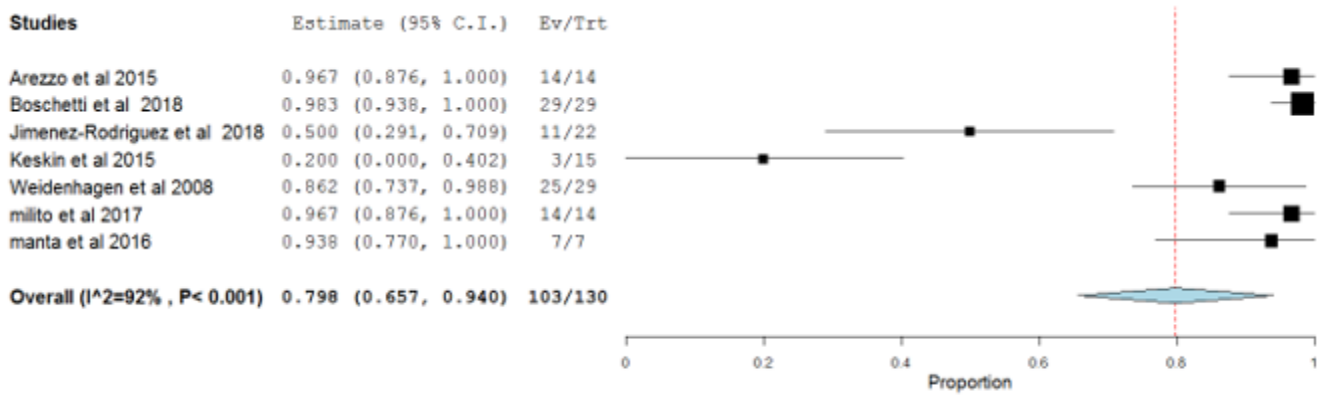
Long term success rate Long term success was recorded for 89 patient. Of these 72/89 (80.9%) were reported as having long term successful healing of AL. Binary random-effects meta-analysis showed that the mean long term success rate across the studies was 84.8% (95% CI 74.8 to 94.7) (I^2 =51).



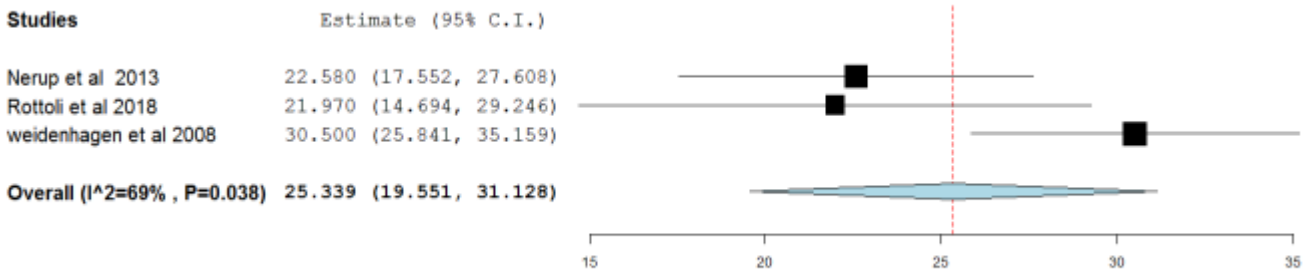
Treatment duration Continuous random effects showed that the weighted mean duration of treatment was 38.1 days until closure of leak (95% CI 30.1 to 46.1 days) I^2 = 94%.



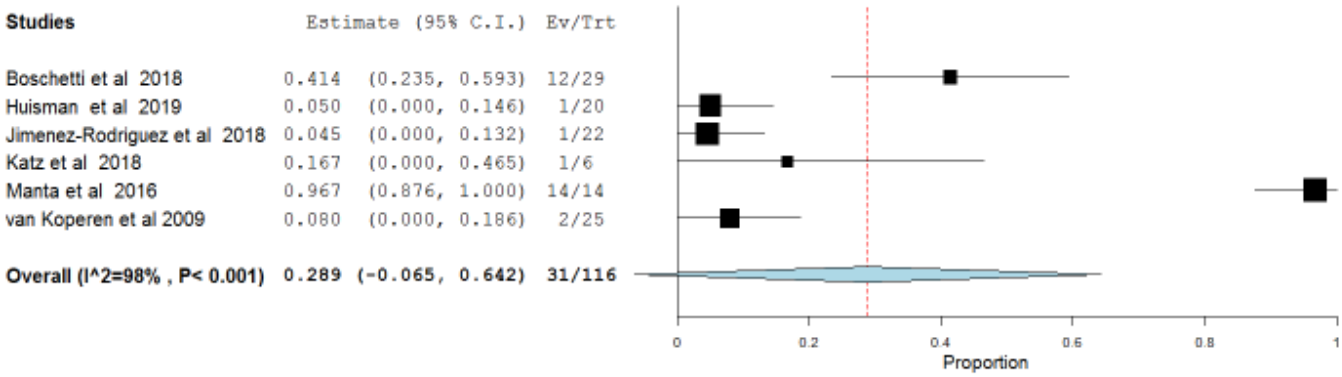
Outpatient use of Endo-SPONGE In or out patient use of Endo-SPONGE was discussed for 124 patients with 103/130 (79.2%). Binary random-effects meta-analysis showed that the weighted mean 79.8% of patient were treated as out patients (95% CI 65.7 to 94.0%) (I^2 =92%).



In Patient LOS was discussed in only 3 journal articles. Continuous random effects showed that the weighted mean LOS was 25.2 days (95% CI 19.6 to 31.1 days) (I^2 = 69%).



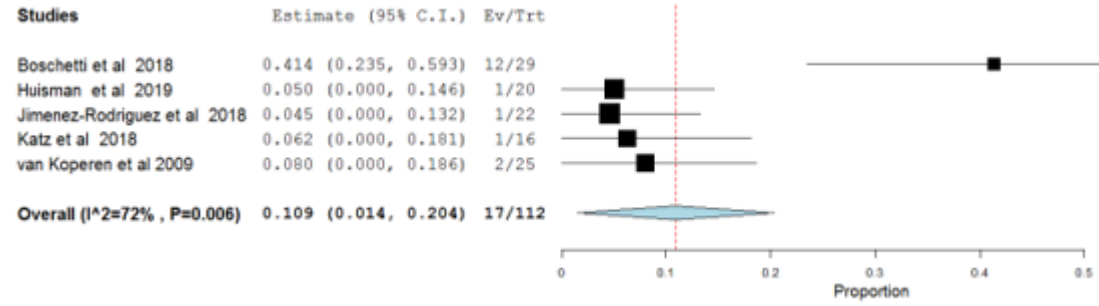
Antibiotic use with/before Endo-SPONGE. Overall 6 studies covering 116 patients discussed use of antibiotics before or during Endo-SPONGE use. Overall 31/116 (26.7%) patients were prescribed antibiotics alongside/ before use of Endo-SPONGE. Binary random-effects meta-analysis showed that the weighted mean 28.9% of patient were treated with antibiotics alongside/before Endo-SPONGE use (95% CI -6.45 to 64.2%) (I^2 =98%). In one study (Katz et al 2018) they had a standard treatment policy for use of antibiotics, rather than use of antibiotics depending on clinical needs n=14/14, this anomalous treatment process may have skewed the data .



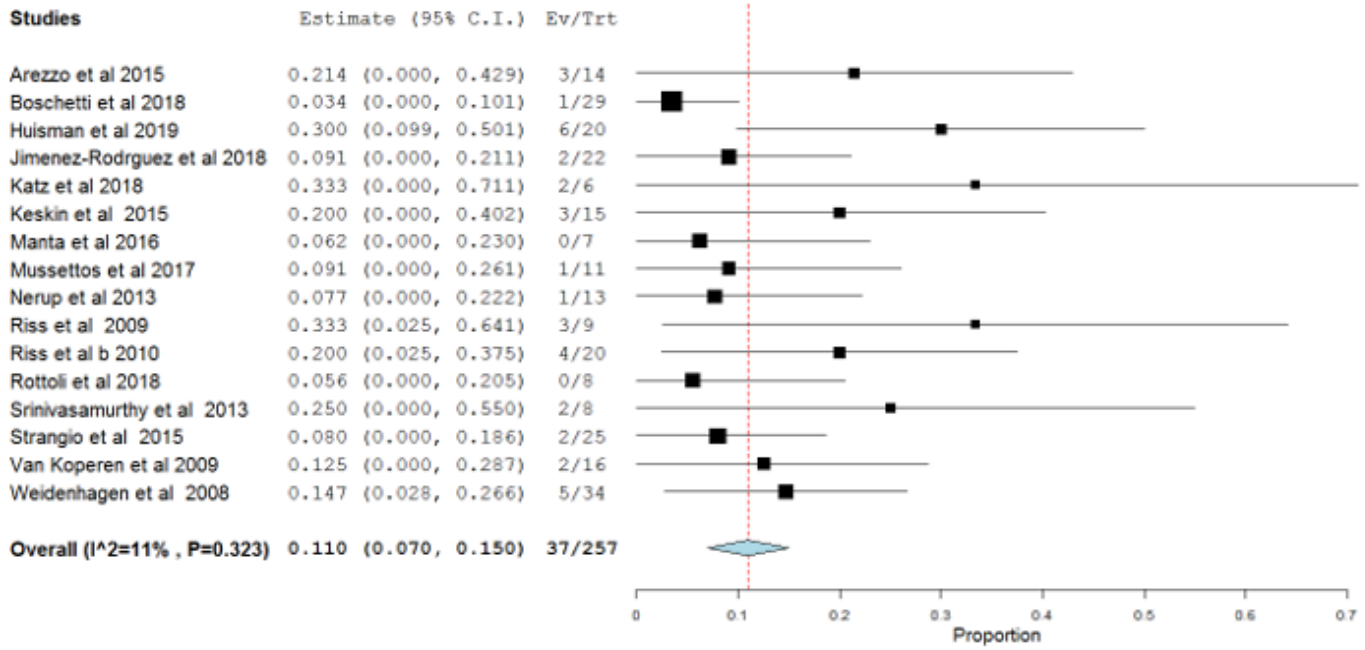
In 2 papers, n=13/49 (26.5%) patients were given antibiotic treatment before Endo-SPONGE treatment commenced.

In 4 papers n= 18/67 (26.86%) patients were treated with antibiotic treatment during Endo-SPONGE treatment. In one study (Manta et al 2016) they had a standard treatment policy for use of antibiotics, rather than use of antibiotics depending on clinical needs, this anomalous treatment process may have skewed the data.

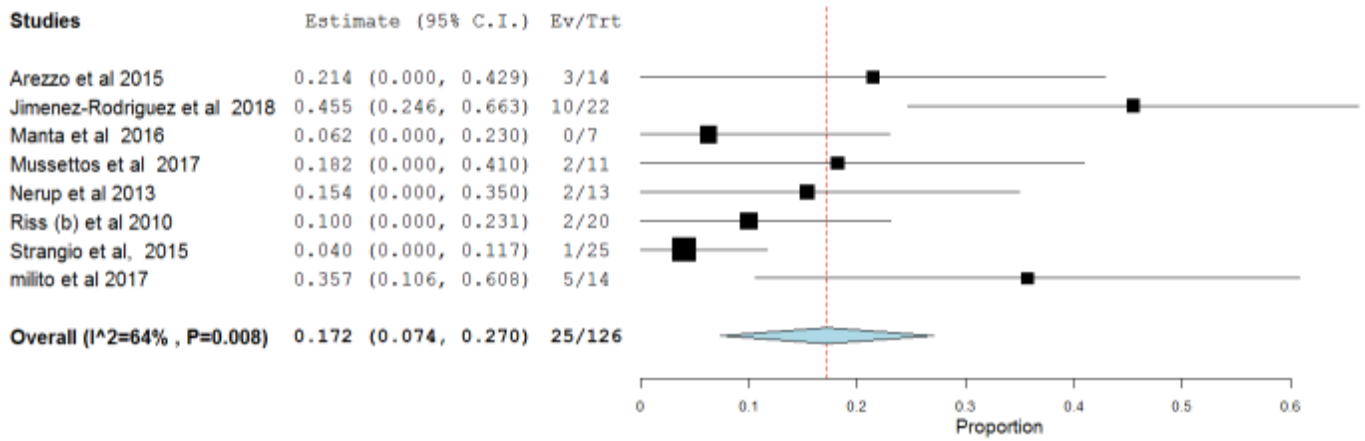
Antibiotic use with Endo-SPONGE – clinician choice. Clinicians chose to prescribe antibiotics alongside Endo-SPONGE in 5 studies covering 112 patients discussed use of antibiotics before or during Endo-SPONGE use. Overall 17/112 (15.2%) patients were prescribed antibiotics alongside/ before use of Endo-SPONGE. Binary random-effects meta-analysis showed that the weighted mean 10.9% of patient were treated with antibiotics alongside/before Endo-SPONGE use (95% CI 1.4 to 20.4%) (I^2 =72%).



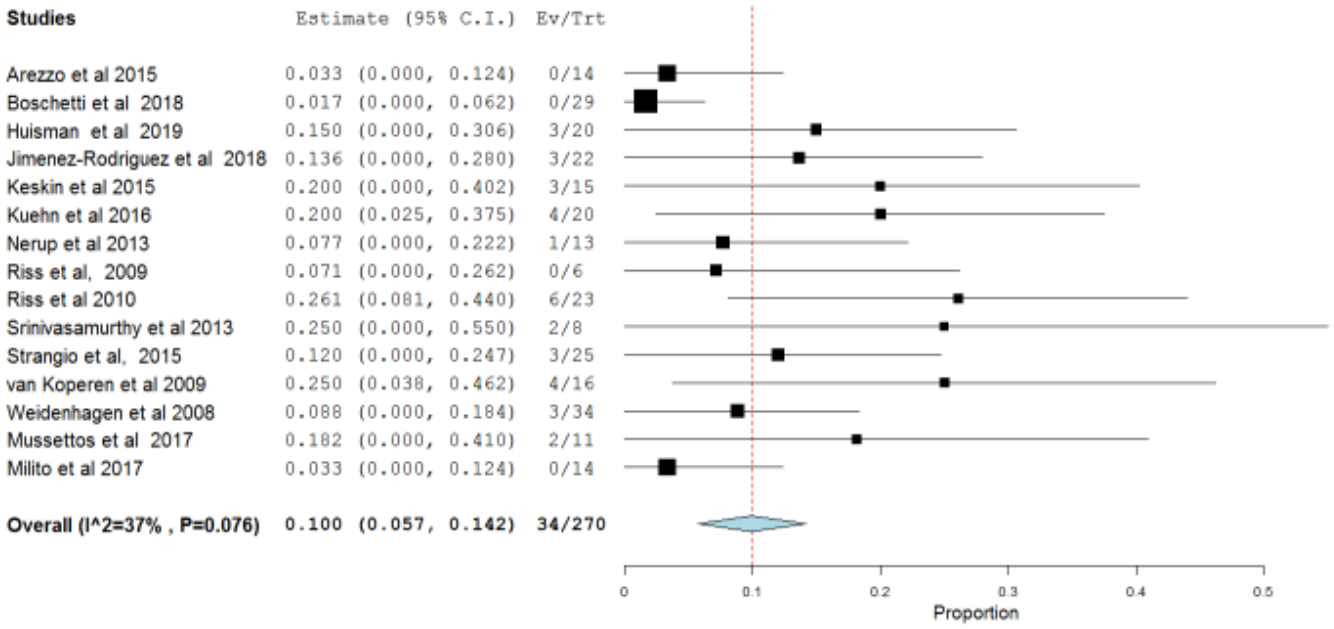
Extra Surgery Required N=37/257 (14.3%) patients required addition surgery with Endo-SPONGE treatment. Binary random-effects meta-analysis showed that the mean additional surgery rate across the studies was 11.0% (95% CI 7.0 to 15.0) (I^2 =11).



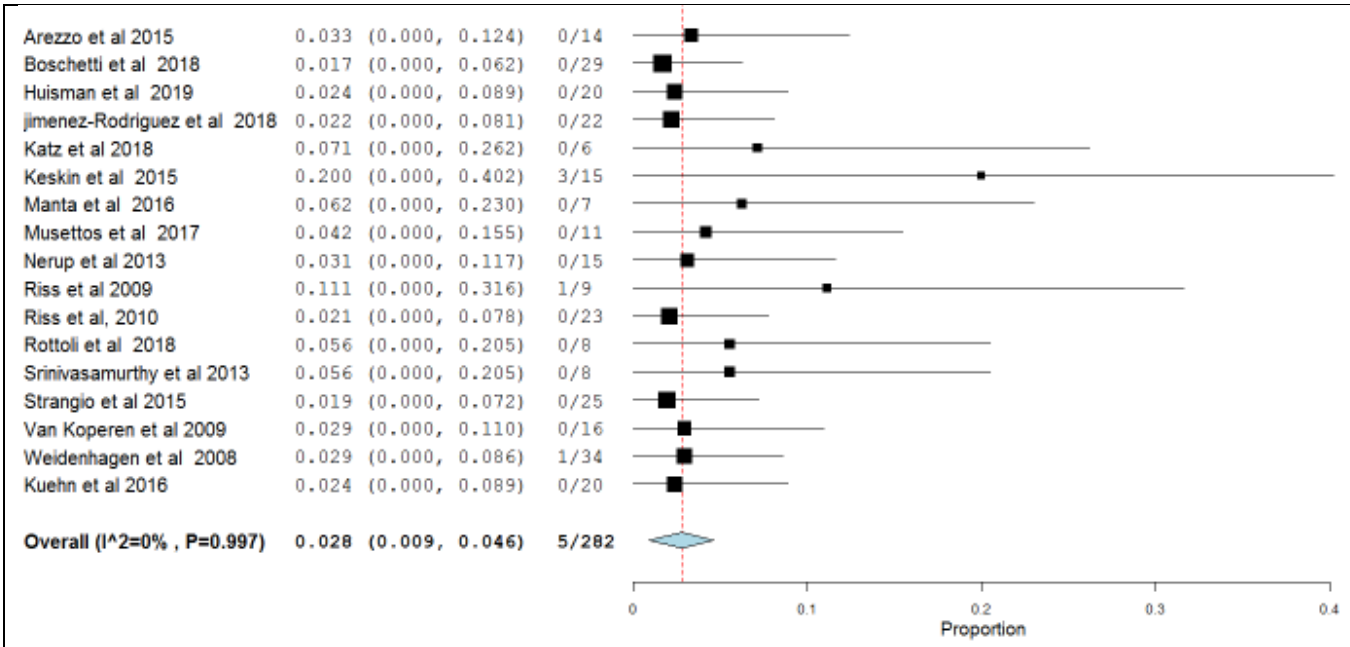
Additional endoscopic treatments in 8 papers use of additional endoscopic treatment was reported in 25/126 (19.8%) in addition to Endo-SPONGE treatment. Binary random-effects meta-analysis showed that the weighted mean use of addition endoscopic treatment was 17.2% (95% CI 7.4 to 27.0) (I^2 =56). Other papers made no mention of complications. Details of extra endoscopic treatment are listed in data abstraction table in appendix A.



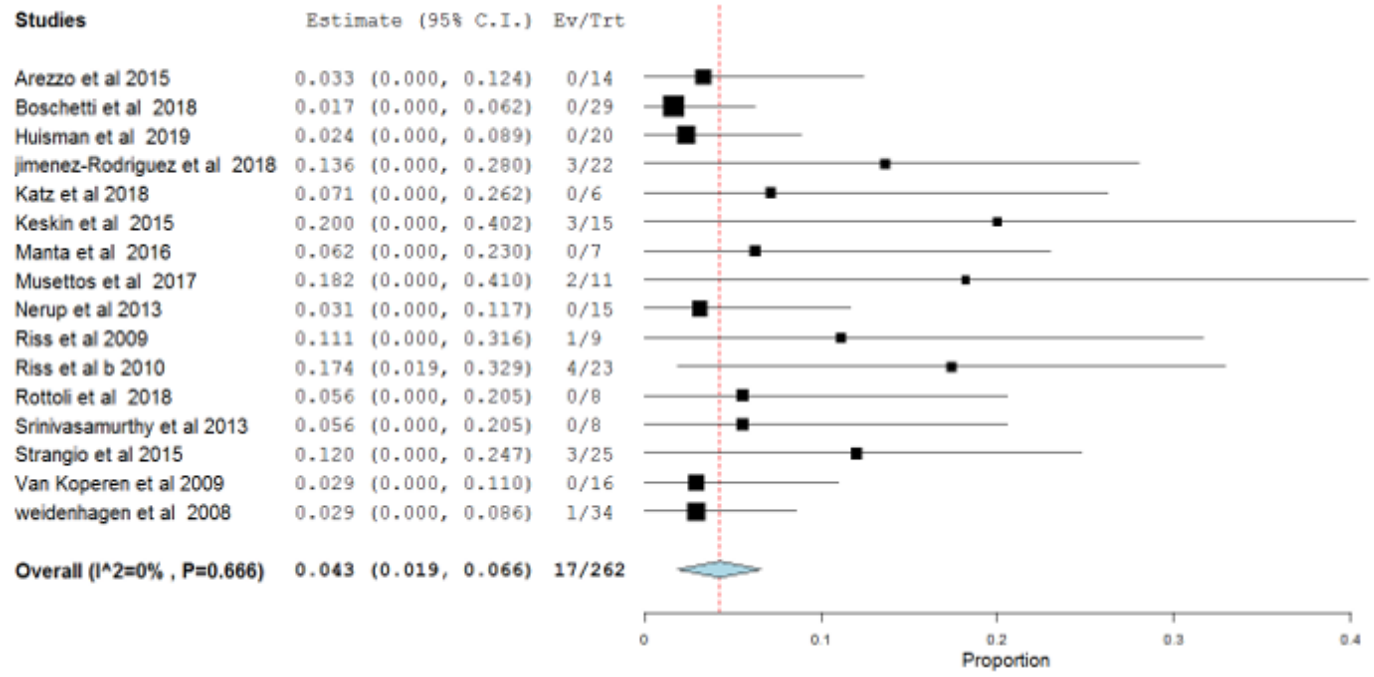
Complication rate N=40/251 (15.9%) developed complications after Endo-SPONGE treatment. Binary random-effects meta-analysis showed that the mean complication rate across the studies was 13.6% (95% CI 7.8 to 19.4) (I^2 =56). Other papers made no mention of complications. Complications are listed in data abstraction table in appendix A.



30 Day Mortality rate overall n=5/282 (1.8%) patients had mortality within 30 days. Binary random-effects meta-analysis showed that the mean 30 day mortality rate across the studies was 2.8% (95% CI 0.9 to 4.6) (I^2 =0).



Overall Mortality overall 17/262 (1.9%) patients died during long term follow up. Binary random-effects meta-analysis showed that the mean 30 day mortality rate across the studies was 4.3% (95% CI 1.9 to 6.66) (I^2 =0).



Explain the main findings and conclusions drawn from the evidence synthesis.

Evidence synthesis here has demonstrated that Endo-SPONGE is highly successful treatment in closing colorectal anastomotic leaks (88.8% success rate.) The resulting stoma reversal rate following Endo-SPONGE is high at 79% within 10.4 months of initial surgery and bowel continuity frequently (70%) being restored. Long term success following Endo-SPONGE is also high (81%). The 30 day mortality rate was low at 2.8% as was the overall long term mortality (4.3%). Mortality rates included deaths not associated to AL (e.g. cranial injury due to falling out of bed and disease progression).

Endo-SPONGE treatment is well tolerated by patients with low (10%) complication rate and short treatment duration (30-46 days), which can be carried out in the outpatient setting for appropriate patients (65-94%).

Use of additional treatments were low with use of Endo-SPONGE: with only 11% of patients using antibiotics alongside Endo-SPONGE, additional endoscopic treatments, when reported occurred in 17% of patients and the need for additional surgery was very low (11%).

Endo-SPONGE offers the opportunity for patients to be treated as an out-patient with up to 79.8% of patients treated as out patients in some studies, depending in patient overall condition.

Qualitative review

Please only complete this section if a quantitative evidence synthesis is not appropriate.

Explain why a quantitative review is not appropriate and instead provide a qualitative review. This review should summarise the overall results of the individual studies with reference to their critical appraisal.

Data on the following parameters are limited and as such not applicable to quantitative review and shall be discussed qualitatively here.

Preventative stoma

Details pertaining to impact of protective stoma were discussed in three papers. In Arezzo et al (2015), 14 patients were treated with Endo-SPONGE of which 8 had a protective stoma created during initial surgery. Following AL a further 3 patients had a stoma created after the detection of an AL. All of the 8 patients with an initial protective stoma were successful for closure of the AL. Of the remaining 6 patients who did not have an initial protective stoma, 3 had no stoma at all and 3 had a stoma created after AL diagnosis, of these six patients, n= 3/6 (50%) were successful in closure of the AL, however details pertaining to presence or absence of a stoma was not disclosed and impact cannot be ascertained from the data.

Boschettis et al (2018) discuss no impact of early stoma on outcome following Endo-SPONGE treatment, with 21/29 patients having a protective stoma and a success rate of 19/21 (90%), all of the 8 patients without a protective stoma were successful in AL healing.

The impact of a protective stoma with regards to Endo-SPONGE success in healing AL cannot be determined from current studies. Use of protective stomas should be used as determined by literature looking into impact of using protective stoma.

Time to AL detection.

Arezzo et al grouped patients for onset/diagnosis of AL, 'early', defined as diagnosis < 60 days post-surgery (n=10/14, 71%) and late defines as diagnosis >60 days post-surgery (n=4/14, 29%). Overall successful healing was observed in 11/14 (79%) of patients. Successful AL closure in the 'early' groups was n=9/10 (90%) and in the 'late' group success was achieved in n=2/4 (50%). No significant impact of early/late onset/diagnosis of AL and healing rate was observed (p=0.18).

Boschetti et al 2018 reported early AL diagnosis in n=12/29 (41%) patients, with 'early' defined as within 30 days, and the remaining n=17/29 (59%) in the 'late' diagnosis group diagnoses after 30 days with a mean time to diagnosis of 35 ± 56 days. The authors determined that there was no correlation between time of AL discovery and closure of leak (Rho=0.45, p=0.12) with Endo-SPONGE.

Early and late detection of AL with respect to Endo-SPONGE treatment outcome was also reported by Keskin et al (2015) with 8/15 (53%) leaks detected within 30 days and 7/15 (47%) detected after 30 days. Overall success was achieved in 12/15 (80%) of patients with 6/8 (75%) in the early group and 6/7 (80%) in the late group.

Overall, studies on the impact of Endo-SPONGE timing offer no definitive answer due to data limitation, although they seem to indicate that early treatment increases the success rate. There is no evidence that a later use of Endo-SPONGE would be beneficial to the patients.

Time to Endo-SPONGE initial placement

In a study involving 20 patients Huisman et al report 10/20 (50%) patients were treated 'early' defined as treatment within 20 days of initial surgery. The other half were treated with Endo-SPONGE 'late', defined as treatment after 21 days following initial surgery. Overall success was 17/20 (80%) and no difference was seen between the two groups, 8/10 (80%) early, 9/10 (90%) late treatment.

Another study by Jimenez-Rodriguez et al (2018) discussed briefly impact of onset of Endo-SPONGE treatment before (15/22, 68%) or after 6 weeks (7/22, 32%) , report a positive impact of therapy success with treatment within 6 weeks compared to more delayed treatment (p=0.041) , although no further details were provided and the study was only small.

Studies on the impact of timing of Endo-SPONGE offer no definitive answer due to limited results. There is no indication that late use of Endo-SPONGE would not be beneficial to patients.

Sepsis

Katz et al 2018 report in 6 patients that sepsis control was achieved in all (100%) of patients following antibiotics, Endo-SPONGE and diversion. Kuehn et al 2016 report local control of sepsis with Endo-SPONGE in 18/20 (90%) of AL leaks following rectal resection and in 9/12 (75%) of patients with Hartmann's stump insufficiency – overall 27/32 (84%). Arezzo et al 2015 reported one case of sepsis developing (1/14, 7%), Keskin et al 2015, report n= 2 cases (13%) of sepsis developing and Von Koperan et al 2009 report no cases of sepsis developing in a group of 16 patients.

8 Summary and interpretation of clinical evidence

Summarise the main clinical evidence, highlighting the clinical benefit and any risks relating to adverse events from the technology.

Endo-SPONGE as a treatment is highly successful in closing colorectal anastomotic leaks, having a 88.8% success rate, which when compared with the 57.4% non-operative success rate for current treatment pathways (appendix B), it demonstrates an improved success rate.

Use of additional treatments were low with use of Endo-SPONGE: with only 11% of patients using antibiotics alongside Endo-SPONGE, when left to clinician decision compared with 51.5% of patients from the current clinical pathway meta-analysis (appendix B). Addition endoscopic treatments, where reported to occur in 17% of patients, treated with Endo-SPONGE

The need for additional surgery is very low (11%) following Endo-SPONGE treatment compared with 42.6% in current clinical pathway meta-analysis (Appendix B).

The resulting stoma reversal rate following Endo-SPONGE is high at 79%, higher than stoma reversal following current non-operative treatment (62.1% Appendix B) and even following all current treatment pathways (54.5% Appendix B). Bowel continuity is frequently (70%) being restored following Endo-SPONGE treatment.

Long term success following Endo-SPONGE is high (81%). Details pertaining to ling term success in the current clinical pathway could not be determined.

The 30 day mortality rate is low at 2.8%, lower than current treatment pathway (10.9% all current treatments appendix B). The overall long term mortality was also low following Endo-SPONGE treatment (4.3%). Mortality rates included deaths not associated to AL (e.g. cranial injury due to falling out of bed and disease progression).

Endo-SPONGE treatment is well tolerated by patients with low (10%) complication rate. Discomfort/pain can be experienced by patients and is reported as well tolerated and easily managed with pain medication. Minor bleeding can occur upon removal of the Endo-SPONGE and was reported to resolve quickly.

Endo-SPONGE has a short treatment duration (30-46 days), which can be carried out in the outpatient setting for appropriate patients (65-94%). Paper identified here could not determine current treatment duration for comparison.

Endo-SPONGE represents an innovative therapy concept for the treatment of anastomotic or Hartmann's leakages, with the potential to contribute significantly to the reduction of morbidity and further complications of these patients.

The study of the post-market experience as well as the activities of post-market surveillance, defines an optimal performance of Endo-SPONGE. The analysis of the presented information throughout this document demonstrates that, according to present knowledge since the initial certification, no unknown findings concerning state of the art or the performance and safety of Endo-SPONGE have emerge. In

conclusion no results of Endo-SPONGE have been found that would challenge the benefit-risk relationship.

Briefly discuss the relevance of the evidence base to the scope. This should focus on the claimed benefits described in the scope and the quality and quantity of the included studies.

Benefits to the patient

Most of the below parameters have been subject to meta-analysis due to the large number of published journals covering use of Endo-SPONGE, demonstrating the high quantity and quality of the data scientific available supporting use of Endo-SPONGE.

Reduced size of the anastomotic cavity/increased cavity closure rate - Endo-SPONGE as treatment is highly successful in closing colorectal anastomotic leaks with 88.8% success rate (95% CI 85.2-92.4%), based on meta-analysis of 17 published articles. This is an improvement in closure rate of AL's compare with current non-operative treatment success rate (57.4%) (appendix B)

Reduced reoperation requirements. The need for additional surgery was low with weighted mean of 11% of patients requiring additional surgery based on data from 16 studies covering 257 patients. This is lower than the calculate re-surgery with conventional treatment at 45.3% (Appendix B).

Low complication rate - Meta-analysis submitted here (section 7) demonstrates weighted mean 10.0% complication rate following Endo-SPONGE treatment from 15 published journals.

Reduced number of permanent stomas- Stoma reversal following Endo-SPONGE treatment, based on 13 published studies demonstrated a weighted mean of 79% success (95% CI 72-86%). This is higher than stoma reversal rate compared with current non-operative treatment (22.1% Appendix B) and when compared to stoma reversal rate from all current treatment options (success rate of 54.5%) (Appendix B).

Reduced risk of subsequent infection if the area is not infected - Arezzo et al 2015 reported one case of sepsis developing (1/14, 7%), Keskin et al 2015, report n= 2 cases (13%) of sepsis developing and Von Koperan et al 2009 report no cases of sepsis developing in a group of 16 patients.

Rapid control of the infection if the area is infected - Katz et al 2018 report in 6 patients that sepsis control was achieved in all (100%) of patients following antibiotics, Endo-SPONGE and diversion. Kuehn et al report local control of sepsis in 18/20 (90%) of AL following rectal resection and in 9/12 (75%) of patients with Hartmann's stump insufficiency – overall 27/32 (84%).

Faster healing compared with conventional treatment - treatment duration with Endo-SPONGE from 13 papers demonstrate a mean duration of 38 days (95% CI 30-46 days). Treatment duration is not clear from literature based on current treatment pathway.

Outpatient option for treatment. Depending on the individual patient, treatment as an outpatient may be option for up to 79% of patients. This is based on data from 7 published journal articles.

Improvement in quality of life – Bowel continuity was restored in 72% of patients (95% CI 57-88%) from 5 published journals. Long term success rate, i.e. low relapse rate, was observed in 85% of patients (95% CI 75-95%) based on 5 published journals. Other evidence pertaining to quality of life is lacking,

however a reduction in the need for extra surgery will be beneficial to patient quality of life, as will the reduced number of patients with a permanent stoma and the option for outpatient treatment.

The benefits to the healthcare system claimed by the company are:

Reduced requirement for reoperation The need for additional surgery was low with weighted mean of 11% of patients requiring additional surgery based on data from 16 studies covering 257 patients, lower than current re-surgery rate of 44.8%, reducing costs of extra surgery and the associated hospital stay.

Reduced stoma consumables and associated costs of complications due to decreased number of permanent stomas. Stoma reversal following Endo-SPONGE treatment, based on 13 published studies demonstrated a weighted mean of 79% success (95% CI 72-86%). Current stoma reversal following current non-operative treatment is 62.1% (Appendix B) and even following all current treatment pathways (54.5% Appendix B).

Reduced resource use (i.e. fewer staff needed) - treatment in outpatient endoscopy or ambulatory setting was reported for 79% (n=103) of patients in 7 studies. While patient dependant, treatment and placement in outpatient require less resource than using a theatres.

Identify any factors which might be different between the patients in the submitted studies and patients having routine care in the UK NHS.

No difference – patients in studies are of the target patient demographic in the UK covering a range of colorectal surgeries which would be applicable in the NHS.

Describe any criteria that would be used in clinical practice to select patients for whom the technology would be most appropriate.

The association of great Britain and Ireland grade AL's 1-5 (F D McDermott et al. 2016). Grade 1, no sepsis, Grade 2a Sepsis with contained leak/abscess <3 cm, Grade 2b Sepsis with contained leak/abscess> 3cm, Grade 3 Sepsis, ileus single quadrant peritonitis , Grade 4 Severe sepsis, more than 1 quadrant peritonitis, and Grade 5 Septic shock, generalised peritonitis. From these definitions AL's grade 1-2b would be applicable (patient dependant) for treatment with Endo-SPONGE, as per the individual surgeon's medical consideration of the whole patient health status.

Asteria et al 2008 classify AL's 1-4 (grade 1 Limited leakage with small adjacent abscess; mild clinical signs (40.5%), grade 2 Small lateral anastomotic failure with adjacent unilocular abscess (approximately 5 cm diameter or greater) (32.9%) grade 3 Failure of half or more of the circumference of an anastomosis (21.5%) and grade 4 Multiocular abscess or peritonitis (5.1%).

The meta-analysis of the scientific literature here indicates that 67.2% of all AL' could be treated with Endo-SPONGE this would cover all grade 1 (according to Asteria) and an estimate of 50% of patients in grade 2 and grade 3 dependent on patient and individual surgeon clinical opinion.

Briefly summarise the strengths and limitations of the clinical evidence for the technology.

The strength of the clinical evidence here is the accumulative number of patient treated with Endo-SPONGE, considering the limitations of the frequency of AL occurrence. Together the large number of studies have been able to be analysed quantifiably by meta-analysis for the majority.

The main limitation of these studies is the lack of controlled studies – due to the nature of low occurrence of AL it is difficult to get large patient studies with any treatments, making controlled studies even more difficult to arrange and that many of the studies are retrospective.

9 References

Please include all references below using NICE's standard referencing style.

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10 Appendices

Appendix A: Search strategy for clinical evidence

Describe the process and methods used to identify and select the studies relevant to the technology. Include searches for published studies, abstracts and ongoing studies in separate tables as appropriate. See section 2 of the user guide for full details of how to complete this section.

Date search conducted:	5.9.19
Date span of search:	Conception to 5.9.19

List the complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean). List the databases that were searched.

Set#	Searched for TX	Results		
		CINAHL Complete, Medline Complete, Biomedical Reference Collection and STM	**Cochrane Library**	**Pubmed**
S1	Endo-SPONGE	162	1	25
S2	Endo-SPONGE	154	2	20
S3	Endoscopic vacuum therapy	3,829	8	337
S4	Endoscopic vacuum-assisted	1,181	10	89
S5	Transanal vacuum therapy	278	1	10
S6	ETVARD	18	0	2
S7	S1 OR S2 OR S4 OR S4 OR S5 OR S6 6	4,159	13	381
S8	Rectum	296,886	-	73,827
S9	Colorectal	750,866	-	165,477
S10	Rectal	428,841	-	114,688
S11	anorectal	40,733	-	11,163
S12	S8 OR S9 OR S10 OR S11	1,152,925	-	287,097
S13	Anastomotic leak	31,530	-	6261
S14	S7 And S12 AND S13	605	13	32
S14	S14 NOT eosophagus	257		

Total = 302

Brief details of any additional searches, such as searches of company or professional organisation databases (include a description of each database):

Previous company search Date: 24th December 2018 and 2nd January 2019
EMBASE and Google Scholar Endo-SPONGE or Endo-SPONGE
Limitations:

- Time period: 2012 – January 2019
- English and Spanish language

Papers not already included in initial search n= 13. These papers were included at stage for full paper analysis

Inclusion and exclusion criteria:

Inclusion criteria	
Population	Lower gastrointestinal tract anastomotic leaks.
Interventions	Endo-SPONGE alone.
Outcomes	Success of stopping leak and time taken. Closure of protective stoma and time taken. Complication rate.
Study design	Systematic reviews, randomised, non-randomised, cohort, observational Case series, Case studies and qualitative studies.
Language restrictions	No language restrictions.
Search dates	5.9.19
Exclusion criteria	
Population	Upper gastrointestinal tract anastomotic leaks
Interventions	Endo-SPONGE in conjunction with other interventions (early surgical closure, over scope clips etc.). Any non Endo-SPONGE endoscopic vacuum therapy. Any other intervention other than endoscopic vacuum therapy. Used outside of device instructions for use (e.g. colonoscopy perforation).
Outcomes	
Study design	Testimonials, non-systematic reviews containing no primary data, editorials, reports describing product news. In vitro studies.
Language restrictions	Unable to obtain translation.
Search dates	5.9.19

Data abstraction strategy:
Data extracted: • Number of participants. • Protective stoma/ stoma after AL detection • Early/ late anastomosis detection/treatment initiation • Frequency of Endo-SPONGE change. • Number of Endo-SPONGE sessions. • Time to healing/duration of therapy. • Success of treatment. • Stoma reversal rate. • Time to stoma reversal. • Complication rate. • Sepsis after treatment • Costs and costs notes • Rate of bowel continuity. • Antibiotic use as well • Abscess size. • 30 day Mortality rate/long term mortality. • Length of stay. • In/Out patient treatment. • Long term success rate. • Need for extra surgery. • Additional endoscopy procedures • Quality of life • Comments

Data Abstraction

Study	N	Protective stoma n (%) stoma after AL	Earl / late anastomosis, treatment initiation	Frequency of changing sponge	Median number of sessions (range) mean ± SD	Median duration of therapy in days/ (range) mean ± SD	Success of treatment (%)	Stoma reversal	Time to stoma reversal	Complications (%)	Sepsis after treatment n (%)	Costs and cost notes
Arezzo et al, (Arezzo et al. 2015a) 2015	14	8/14 (57) yes 6/14 (43) no N= 3 diverted after AL identified	10/14 (71) acute (early) <60 days 4/14 (29%) chronic (late) > 60 days Diagnosis	2-3 times per week	12.5 (4-40)	40.5 (8-114)	11/14 (78.5) overall 9/10 (90%) acute (early)leaks 2/4 (50%) chronic (late) leak (p=0.18) 8/8 (100%) with stoma initially 3/6 (50%) No stoma initially (p=0.055) 8/10 (80%) 25% leak 1/1 (100%) 50% leak 2/3 (66%) 75% leak	N/A	N/A	0/14 (0)	1/14 (7) overall developed sepsis 1/10 (10) acute 0/4 (0) Chronic	180 Euro/device 70 Euro (15 min endoscopy 1 Dr 1 nurse) median cost 3125 (1,000-10,000)
Boschetti et al 2018	29	21/29 (72) yes 8/29 (28) no N=0 diverted after AL identified	12/29 (41) early < 30 days 17/29 (59) >30 days Diagnosis	Every 3-5 days	18.6 (4-57)	70 (14-196) overall 70 (14-196) with stoma 56 (14-98) No stoma	27/29 (93) overall 19/21 (90) With stoma 8/8 (100) No stoma No correlation to time of AL discovery and closure (Rho=0.45 p=0.12)	18/21 (87.5)	After 6 months 18 patients (85.7%) had reversal	0/29 (0)	N/A	Treatment without sedation as out patient
Huisman et al 2019	20	14/20 (70) yes 6/20 (30) no N=4 diverted after AL detected	10/20 (50) early 10/20 (50) late Treatment NOT diagnosis	Change 2x per week	9 (2-28)	25 (3-115) All 20 (3-115) early 25 (5-80) late p=0.79	17/20 (80%) all 8/10 (80) early 9/10 (90) late	14/18 (77.8%)	10 mo(3-15) all 7 (3-11) early 10 (6-15) late p=0.15	chronic sinus 3/20 (15) all 2/10 (20) early 1/10 (10) late	N/A	N/A
Jimenez-Rodriguez et al 2018	22	13/13 (100) yes following LAR N= 0 diverted after AL identified	15/22 (68) early treatment < 6 weeks 7/22 (32) late treatment > 6 weeks	Every 3-5 days	3.1 ±1.9	22.3 ±14.7	19/22 (86) Onset of therapy <6weeks p=0.041 (no data) Cavity size p=0.226	5/13 (38.5%) ileostomy	N/A	0/22 during treatment 3/22 after treatment (13.6) n=1 stenosis, n=1 chronic fistula, n= 1 osetomylitis	N/A	Cost for ambulatory stay/day US$80
Katz et al 2018	6	3/6 (50) yes 3/6 (50) no N= 2 diverted after AL identified	6/6 (100) early < 14 days, treat < 17 days	N/A	N/A	N/A	6/6 (100)	4/5 (80) 1/5 new tumour prevented closure	N/A	N/A	6/6 sepsis was controlled	N/A
Keskin et al, 2015	15		8/15 (53) early <30 days	Every 3-4 days	2.2 (1-5)	NA	12/15 (80) all 6/8 (75%) early	10/14 (71) n=3 died due to		3/15 (20) n=2 sepsis		N/A

Study	N	Protective stoma n (%) stoma after AL	Earl / late anastomosis, treatment initiation	Frequency of changing sponge	Median number of sessions (range) mean ± SD	Median duration of therapy in days/ (range) mean ± SD	Success of treatment (%)	Stoma reversal	Time to stoma reversal	Complications (%)	Sepsis after treatment n (%)	Costs and cost notes
		N/A	average 15 (6-27d) 7/15 (47) late 173 (43-343d)				6/7 (85%) late	disease progression before closure	N/A	n=1 bleeding	N/A	
Kuehn et al, 2016	20 AL 41 total	19/20 (95) yes AL	N/A	Every 3 days	7(1-37) AL 6 (1-37) total	23 (2-109) AL 20 (2-131) total	18/20 (90) AL 34/41 (83) total	15/19 (79) AL	244 days (152-488 days)	4//20 (15) N=1 bleeding N=3 stenosis	27/32 sepsis controlled	N/A
Manta et al 2016	7	N/A	1/7 (14) early 6/7 (86) late	N/A	N/A	N/A	7/7 (100)	N/A	N/A	N/A	N/A	N/A
Milito et al 2017	14	14/14 (100) yes protective stoma	14 (7-21)days AL detected		3-14	35(16-51) treatment 37 (19-55) healing time	N/A	N/A	N/A	0/14	N/A	N/A
Mussettos et al 2017	11	N/A	N/A	Every 2-3 days	16 (9-23)	37 (18-65)	10/11 (91)	N/A	N/A	2/11 (18) anastomotic stricture	N/A	N/A
Nerup et al, 2013	13	N/A	N/A	Every 2-3 days	N/A	18 (3-40)	13/13 (100)	12/13 (92%)	N/A	1/13 (7.6) stenosis	N/A	N/A
Riss et al, 2009	6 AL 9 total	1/6 (11) yes protective stoma AL N=3 diverted after AL identified 2/6 (22) no stoma AL 3/3 (100) Hartmann = stoma	1/9 (11) early = 7 days 8/9 (89) late = 2.5 (1-24mo) for total 8 weeks to LAR AL 10 weeks to Hartmann's leak	Every 2-3	N/A	21 (14-56) total	6/9 (67) total 5/6 (83) AL 1/3 (33) Hartmann's	N/A	N/A	0/6 (0)	N/A	Duration of Endo-SPONGE insertion 15 min (5-65)
Riss et al, 2010	23	14/23 (61) yes N=2 diverted after AL identified	N/A	Every 2-3 days	N/A	21 (range 7-106)	20/23 (87) initial	13/17 (76.5)	N/A	6/23 (30) long term complications N=1 stenosis N=5 recurrent abscess	N/A	N/A
Rottoli et al 2018	8	N/A	N/A	Every 2-3 days	3 (1-10)	12 (3-32)	8/8 (100)	7/8 (87.5) 1 pt chose to delay closure	2.5 (1-6) months after closure	N/A	N/A	N/A
Srinivasamurthy et al, (Srinivasa	8		29 (10-115) days to AL detection	NA	4 (1-7)	26 (7-49)	6/8 (75) all	5/8 (62.5)		2/8(25) N=1 fistula		N/A

Study	N	Protective stoma n (%) stoma after AL	Earl / late anastomosis, treatment initiation	Frequency of changing sponge	Median number of sessions (range) mean ± SD	Median duration of therapy in days/ (range) mean ± SD	Success of treatment (%)	Stoma reversal	Time to stoma reversal	Complications (%)	Sepsis after treatment n (%)	Costs and cost notes
murthy et al. 2013b) 2013		N/A	5/8 (62.5) < 6 weeks 3/8 (37.5) >6 weeks from surgery to sponge placement						41 months (10-45 months)	n=1 inadvertent placement of Endo-SPONGE	N/A	
Strangio et al, 2015	25	13/25 (52) yes preventative	17 (15-100) days to AL detection 16 (0-53) days from detection to Endo-SPONGE insertion	Every 2-3 days	9 (1-39)	28 (7-128)	22/25 (88)	11/13(84.)	N/A	3/25 (12) N=1 urethirc fistula, n=1 ileal fistula N=1 pararectal abscess	N/A	N/A
van Koperen et al, 2009	16	8/16 (50) yes preventative N=7 diverted after AL identified	11 (3-150) days after AL discovery 8/16 (50) early < 6 weeks 24 (13-39) days 8/16 (50) late > 6 weeks 74 (43-1,602) days	Every 3-4 days	13 (8-17)	40 (28-90)	9/16 (56.2)	5/9 (56%)	N/A	4/16 (25) N=1 bleeding 500 cc N=1 pain stopped therapy N=1 stopped due to near complete dehiscent anastomosis N=1 recurrent abscess.	0/16 developed peritonitis	N/A
Weidenhagen et al, 2008	34 all 29 PP	21/29 yes protective stoma N=3 stoma created after AL detection N=1 stoma created after Endo-SPONGE treatment	8.2±3.6 days after surgery AL discovered	Every 2-3 days	11.4 ±6.3 (range 1-27)	34.4 (4-79)	28/34 (82.3)	22/25 (88)	168.9±81.7 days	3/34 N=2 ischemic necrosis N=1 rectovaginal fistula	N/A	N/A
Total	315	N/A	N/A	N/A	N/A	N/A	238/277 (85.9%)	141/183 (77.0%)	N/A	34/270 (12.6)	N=1 sepsis developed /54	N/A
weighted mean 95% CI	N/A	N/A	N/A	N/A	10.7 (8.0-13.5)	38.1 (30.1-46.1)	88.8 (85.2-92.4)	79.0 (71.9-86.1)	10.41 month (7.05-13.77)	10.0 (5.7-14.2)	N/A	N/A

Study	N	bowel continuity	Antibiotics as well	Abscess size cm (mean, median)	Distance from anal verge	Mortality 30d/ long term	LOS days	In/out pt	Long term success	Need for extra surgery	Additional endoscopic treatment	Quality of life
Arezzo et al, (Arezzo et al. 2015a) 2015	14	N/A	N/A	5.0 4cm (2-9)	N/A	0/14	7 days for 10/14	4/14 all OP 14/14 OP after 7 days	N/A	3/14 (21.4%) diverting stoma created	2/14 (14.3%) OTSC 1/14 (7.1%) Glue	N/A
Boschetti et al 2018	29	N/A	12/29 (41%) b4 endo – stopped by d 10	7.0 7±4.6cm (2-20cm)	6.2±4.6cm (2-20cm)	0/29	N/A	29/29 out patients	24/29 (83%)	1/29 definitive end stoma	N/A	N/A
Huisman et al 2019	20	14/20 (70) all 7/10(70) early 7/10(70) late	n=1 before endo treatment	N/A	8.5cm (5-12cm)	0/20	N/A	N/A	N/A	6/20 (30%) definitive stoma n=3, n=1 proctectomy, n=1 recurrence n=1 tumour progression	N/A	Increased LARS (endo sponge + AL) 37 (23-42) versus no AL 30 (4-41) P=0.009
Jimenez-Rodriguez et al 2018	22	5/13 (38.5)	1/22 (4.5%)	5.9±1.9cm ALL 5.3±1.8cm LAR 6.6 ±2.1cm Hartmann	4.92±1.9cm	0/22 3/22(13) died long term follow up	N/A	11/22 outpatients	15/22 (68.2%) 4/22 (18.2%) second course of endo n= 3 success 18/22 (81.8%)	2/22 (9.1%)	10/22 (45%) glue after cavity too small for Endo-SPONGE	N/A
Katz et al 2018	6	5/6 (83)	1/6 (16.7%) with endo	N/A	N/A	0/6	N/A	N/A	N/A	2/6 (33.3%) diverting stoma	N/A	N/A
Keskin et al, 2015	15	12/15 (80)	N/A	N/A	N/A	0/15 (0) 30 day follow op 3/15 (20)long term follow up	N/A	3/15 out patient	N/A	3/15 (20%)	N/A	N/A
Kuehn et al, 2016	20 AL	N/A	N/A	N/A	N/A	0/20	N/A	N/A	N/A	N/A	N/A	N/A
Manta et al 2016	7	N/A	N/A	3 median 2.9 mean (1.5-5cm)	N/A	0/7	0 treated as O/P	7/7 outpatient	N/A	0/7	0/7	N/A
Milito et al 2017	14	N/A	14/14	Median 8.1 x4.6cm	N/A	N/A	N/|A	14/14 out patient	N/A	N/A	N/A	N/A
Mussettos et al 2017	11	N/A	N/A	7.5cm (4-12cm)	4.5cm (2-8cm)	0/11 30 d 2/11 (18) long term	N/A	N/A	10/10 (100%)	1/11 (9%) re-op converted to Hartmann's	1/11 dilation 8mo after healing, 1/11 stent 5 mo stent fitted	N/A
Nerup et al, 2013	13	N/A	N/A	N/A	N/A	0/13	25 days (7-39)	N/A	N/A	1/13 reoperated permanent stoma	2/13 moved to conservative treatment	N/A
Riss et al, 2009	9					1/9 heart attack		N/A		3/9 (33)total		Satisfaction 3 (0-9)

Study	N	bowel continuity	Antibiotics as well	Abscess size cm (mean, median)	Distance from anal verge	Mortality 30d/ long term	LOS days	In/out pt	Long term success	Need for extra surgery	Additional endoscopic treatment	Quality of life
		N/A	N/A	N/A	N/A		N/A		N/A	N=resection after Hartmann's N=Hartmann's after AL	N/A	Altered daily life 5 (1-9) Pain 3 (0-6) Would you repeat treatment 6/9 = yes, 2/9 = no
Riss et al, 2010	23 all 20 PP	N/A	N/A	N/A	N/A	0/23 30 day 4/23 (17) long term follow up	N/A	N/A	15/20 (75%) all	3/20 anastomosis taken down and Hartmann's 1/20 CT guided drainage	1/20 (5%) glue 1/20 (5%) anal stent	
Rottoli et al 2018	8	N/A	N/A	N/A	N/A	0/8	15.5 (6-48) median	0/8 outpatient	8/8	1/8 n=1 loop ileostomy before Endo-SPONGE treatment	N/A	0/8 reported incontinence to faeces or gas. Daytime bowel movement 5 (3-8) night time bowel movement 1.7 (1-4)
Srinivasamurthy et al, (Srinivasamurthy et al. 2013b) 2013	8	5/8(62.5) all 4/5 (80) early 1/3 (33) late,	N/A	N/A	N/A	0/8	N/A	N/A	N/A	2/8 (37.5%) N=1 abdominoperineal excision of rectum, n=1 Hartmann's	N/A	N/A
Strangio et al, 2015	25	11/13 (84)	N/A 2/25 (8%)antibiotics (failed pt)	5.6 (1.5-10.0cm) median	N/A	0/25 30 day 3/25 (12) n=2 cancer n=2 vascular accident	N/A	N/A	N/A	2/25 (8%) re-operation	1/25 (4%) CT guided drainage	N/A
van Koperen et al, 2009	16	N/A	N/A	N/A	5cm (2-8cm)	0/16	N/A	N/A	N/A	2/16 inter sphincteric proctectomy	N/A	N/A
Weidenhagen et al, 2008	34 all 29 PP	N/A	N/A	2 – 20 (7.4±5.1cm)	5.3cm (1-12cm)	1/34 fell out of bed	Mean 30.5±12.8 (10-69)	25/29 outpatient	N/A	5/34 within 1 week/ 1-2 sessions N=1 after Endo-SPONGE treatment N=1 Hartmann's	N/A	N/A
Total	292	47/67 (70.1)	17/112 (15.2)	N/A	N/A	5/262 (1.9) 30d 17/262 (6.5) long term		103/130 (79)	72/89 (80.9)	37/257 (14%)	25/126 (20)	N/A

Study	N	bowel continuity	Antibiotics as well	Abscess size cm (mean, median)	Distance from anal verge	Mortality 30d/ long term	LOS days	In/out pt	Long term success	Need for extra surgery	Additional endoscopic treatment	Quality of life
Meta-analysis weighted mean (95% CI_	N/A	72.1 (56.9-87.3)	10.9 (1.4-20.4)	5.82cm (4.58-7.10cm)		2.8 (0.9-4.8) 30d 4.3 (1.9-6.6) long term	25.3 days (19.6-31.1) Outpatient not included	79.8 (65.7-94)	84.8% (95% CI 74.8 to 94.7)	11.0% (7.0-15.0)		N/A

Excluded studies

List any excluded studies below. These are studies that were initially considered for inclusion at the level of full text review, but were later excluded for specific reasons.

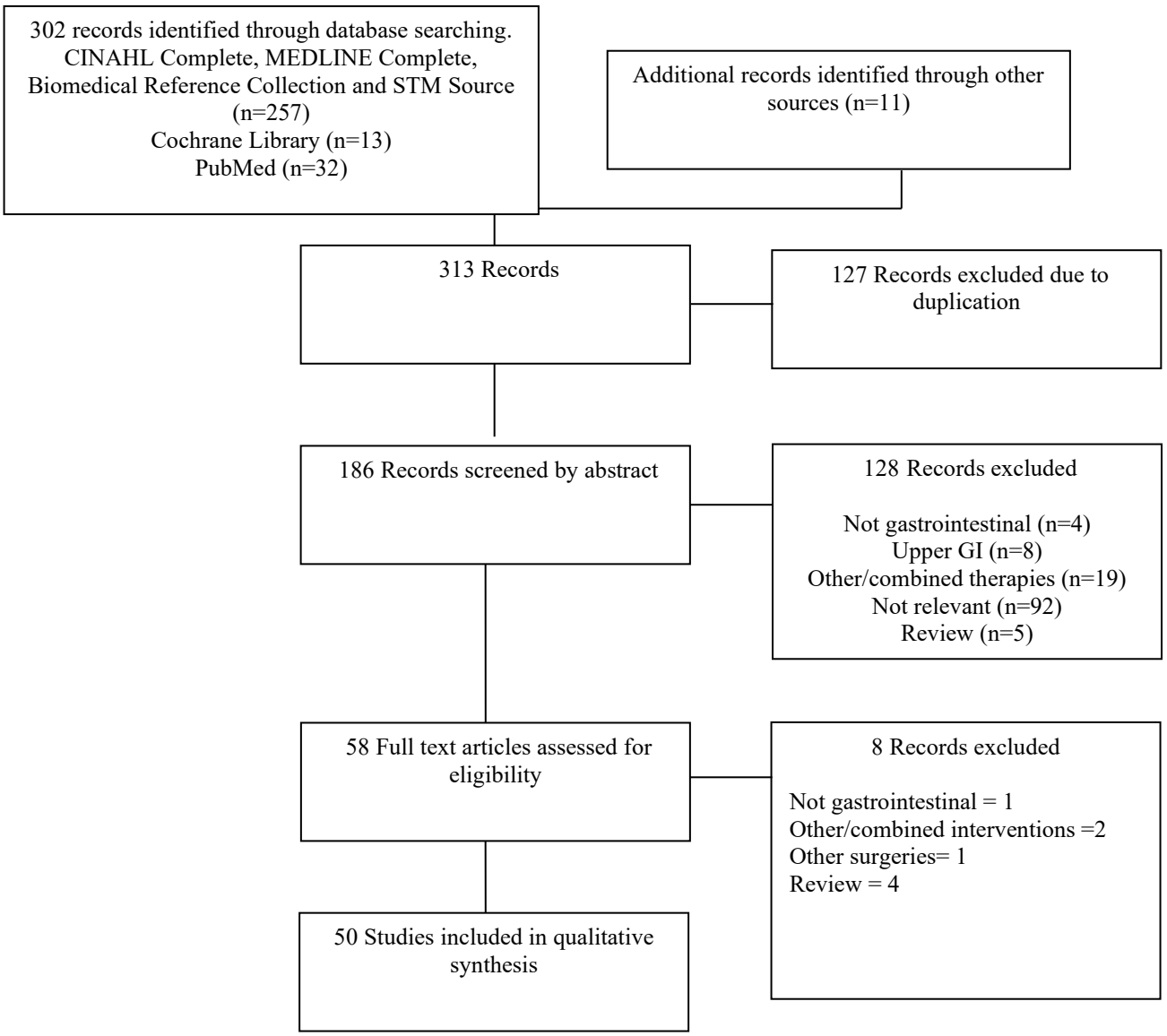
Author	Title	Exclusion reason	Company comments
Arezzo et al 2010	Endoluminal vacuum therapy for anastomotic leaks after rectal surgery	Case studies n=3	Descriptive data only
Bemelman 2009	Vacuum assisted closure in coloproctology	Review	No primary data
Borejsza-Wysocki et al	Endoscopic vacuum-assisted closure system (E-VAC): case report and review of the literature	Use of non Endo-SPONGE device, case study, review	Device used is not CE marked and indicated for use for endoscopic vacuum therapy
Borstlap et al 2018	Vacuum-assisted early transanal closure of leaking low colorectal anastomoses: the CLEAN study	Endo-SPONGE in conjunction with surgical closure	Other therapy – cannot be assured effect from Endo-SPONGE
Chopra et al 2009	The effect of endoscopic treatment on healing of anastomotic leaks after anterior resection of rectal cancer	No primary data for Endo-SPONGE	No primary data
Cirocchi et al 2013	Treatment of Hinchey stage III-IV diverticulitis: a systematic review and meta-analysis.	Not Anastomotic leak	
D'Hondt et al 2010	Chronic pelvic abscedation after completion proctectomy in an irradiated pelvis: another indication for Endo-SPONGE treatment?	Case studies n=1	Descriptive data only
Durai and Ng 2010	Surgical Vacuum Drains: Types, Uses, and Complications	Review, non Endo-SPONGE irrelevant	Device used is not CE marked and indicated for use for endoscopic vacuum therapy
Einkel et al 2011	Sonographic diagnosis and Endo-SPONGE assisted vacuum therapy of anastomotic leakage following posterior pelvic exenteration for ovarian cancer without using a protective stoma	Case study n=1	Descriptive data only
Eriksen 2018	Short- and long-term outcomes after colorectal anastomotic leakage is affected by surgical approach at reoperation	No primary data on Endo-SPONGE	
Gardenbroek et al 2014	Early reconstruction of the leaking ileal pouch-anal anastomosis: a novel solution to an old problem	Endo-SPONGE in conjunction with surgical closure	Other therapy – cannot be assured effect from Endo-SPONGE

Author	Title	Exclusion reason	Company comments
Glitsch et al 2008	Endoscopic transanal vacuum-assisted rectal drainage (ETVARD): an optimized therapy for major leaks from extra peritoneal rectal anastomoses	Use of non Endo-SPONGE device	Device used is not CE marked and indicated for use for endoscopic vacuum therapy
Heeney et al 2010	Vacuum-assisted closure of chronic anorectal fistula	Case studies n=2	Descriptive data only
Hoogenboom et al 2010	Small intestinal-colorectal anastomotic fistula developing during Endo-SPONGE treatment	Case study n=1	Descriptive data only
Knuth et al 2013	Transrectal ultrasound-guided endoscopic drainage and vacuum therapy of pelvic abscesses: an alternative to (computed tomography-guided) percutaneous drainage	Case study n=1	Descriptive data only
Menico et al 2018	Use of a novel technique to manage gastrointestinal leaks with endoluminal negative pressure: a single institution experience	Use of non Endo-SPONGE device	Device used is not CE marked and indicated for use for endoscopic vacuum therapy
Martinotti et al 2014	Combined endoscopic transanal vacuum assisted rectal drainage: A novel therapy for colorectal anastomotic leak after TME for Cancer	Case studies n=4	Descriptive data only
Nagell and Holte 2006	Treatment of anastomotic leakage after rectal resection with trans rectal vacuum-assisted drainage (VAC). A method for rapid control of pelvic sepsis and healing	Use of non Endo-SPONGE device	Device used is not CE marked and indicated for use for endoscopic vacuum therapy
Okoshi et al 2013	Efficacy of transanal drainage for anastomotic leakage after laparoscopic low anterior resection of the rectum	Not vacuum assisted treatment	
Perathoner et al 2010	Damage control with abdominal vacuum therapy (VAC) to manage perforated diverticulitis with advanced generalized peritonitis--a proof of concept	Not anastomotic leak, not Endo-SPONGE	
Richterich 2008	Endo-SPONGE a new endoscopic treatment option in colonoscopy	Use outside of IFU for Endo-SPONGE Case study n=1	
Runkel and Birk 2014	Endoluminal Negative Pressure Wound Therapy (E-NPWT) for anastomotic leakage after rectal resection	Use of non Endo-SPONGE device	Device used is not CE marked and indicated for use for endoscopic vacuum therapy
Shelygin et al 2018	Meta-analysis of management of colorectal anastomotic leakage	Unable to translate	

Author	Title	Exclusion reason	Company comments
Sumrien et al 2016	The use of a negative pressure wound management system in perineal wound closure after extralevator abdominoperineal resection for rectal cancer (ELAPE) for low rectal cancer	Poster abstract	
Terzian et al 2016	Repair of Coloanal Anastomotic Dehiscence and Sinus Formation Using Intraluminal Application of Endo-SPONGE®	Case study n=1, non anastomotic leak	Descriptive data only
Van Koperen et al 2008	Endo-SPONGE treatment of anastomotic leakage after ileo-anal pouch anastomosis: report of two cases	Case studies	Descriptive data only
Verlaan et al 2011	Early, minimally invasive closure of anastomotic leaks: a new concept	Endo-SPONGE in conjunction with surgical closure	Other therapy – cannot be assured effect from Endo-SPONGE
Von Bernstoff et al 2009	ETVARD (endoscopic transanal vacuum-assisted rectal drainage) leads to complete but delayed closure of extra peritoneal rectal anastomotic leakage cavities following neoadjuvant radiochemotherapy	Use of non Endo-SPONGE device	Device used is not CE marked and indicated for use for endoscopic vacuum therapy
Wood, Wright, Witherspoon	Fungal endophthalmitis: an unusual complication of GI surgery and endoluminal vacuum therapy	Case study n=1	Descriptive data only
Worley et al 2018	Management of early pouch-related septic complications in ulcerative colitis: a systematic review	Not Anastomotic leak	

Report the numbers of published studies included and excluded at each stage in an appropriate format (e.g. PRISMA flow diagram).

Response



Structured abstracts for unpublished studies

Study title and authors
Introduction
Objectives
Methods
Results
Conclusion
Article status and expected publication: Provide details of journal and anticipated publication date

No unpublished studies

Appendix B: Search strategy for Current anastomotic leak outcome

Date search conducted:	15.10.19
Date span of search:	Conception until 15.10.19

List the complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean). List the databases that were searched.

Enter text.

Set#	Searched	Results		
		CINAHL Complete, Medline Complete, Biomedical Reference Collection and STM	**Cochrane Library**	**Pubmed**
S1	Anastomotic leak (TI)	1,346	1	401
S2	Anorectal (TX)	41,102	65	10,767
S3	Colorectal (TX)	760,006	348	152,107
S4	Rectal (TX)	432,350	445	112.285
S5	Rectum (TX)	299,056	233	64,992
S6	S2 OR S3 OR S4 OR S5	1,164,841	739	273,656
S7	Outcome* (TX)	8,282,063	7796	2,312,673
S8	S1 AND S6 AND S7	356	1	80
	total	437		

Brief details of any additional searches, such as searches of company or professional organisation databases (include a description of each database):

Inclusion and exclusion criteria:

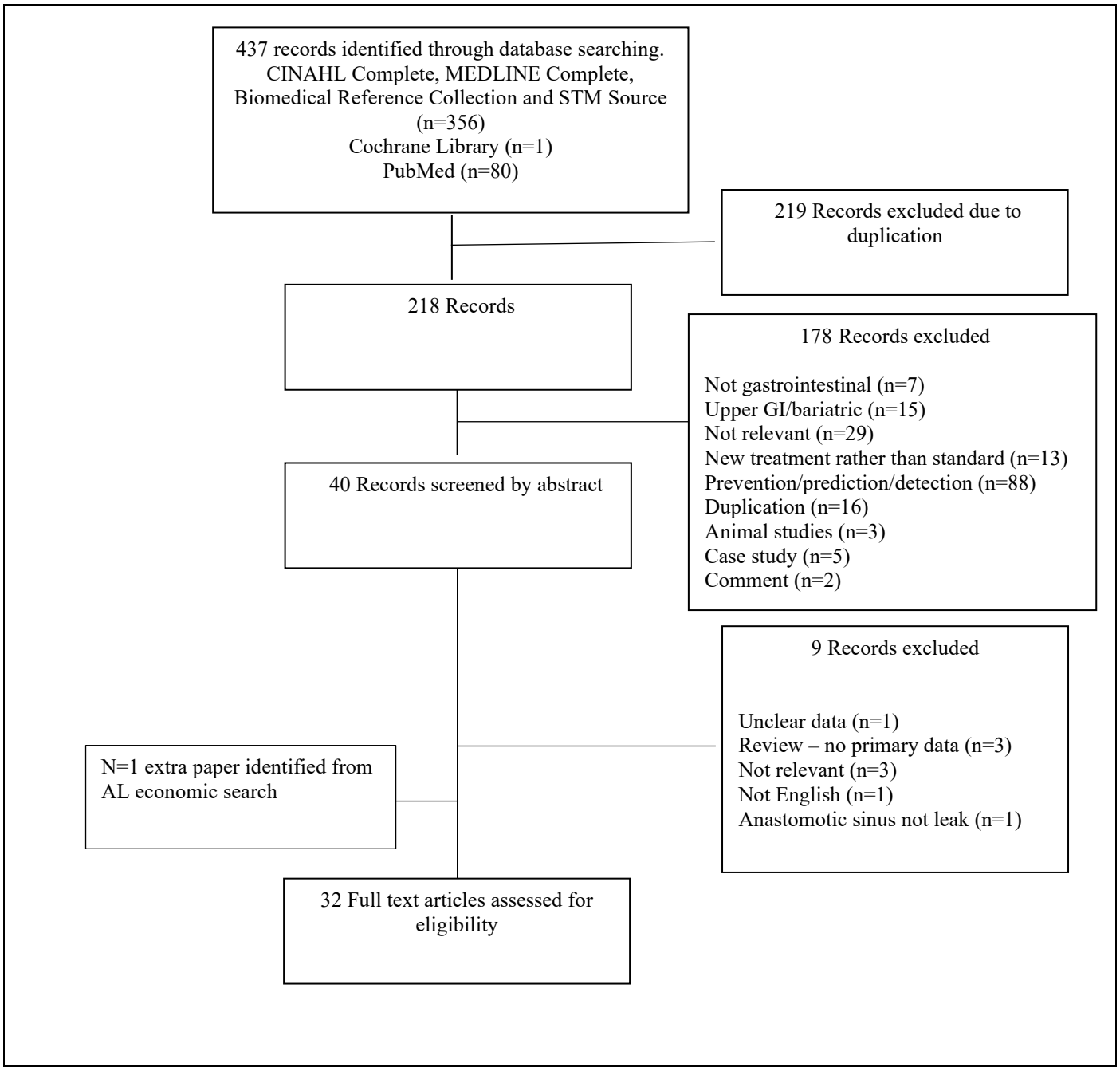
Inclusion criteria	
Population	Lower gastrointestinal tract anastomotic leaks
Interventions	Standard intervention to resolve anastomotic leak (re-operation, non-operative conservative interventions, antibiotics and percutaneous drain)
Outcomes	Success of stopping leak and time taken Closure of protective stoma and time taken 30 day mortality rate Complication rate Length of stay
Study design	Systematic reviews, randomised, non-randomised, cohort, observational Case series, Case studies and qualitative studies.
Language restrictions	No Language restrictions
Search dates	5.9.19
Exclusion criteria	
Population	Upper gastrointestinal tract or bariatric anastomotic leaks, Non gastrointestinal.
Interventions	Interventions to prevent AL Any new test/non-standard treatment of AL Anastomotic sinus
Outcomes	
Study design	Testimonials, comments, non-systematic reviews containing no primary data, editorials, reports describing product news. In vitro or animal studies.
Language restrictions	Unable to obtain translation
Search dates	15.10.19

Data abstraction strategy:

Data Abstracted:

- Incidence of AL
- Intervention used (operative or non-operative)
- Type and rate of non-operative intervention (percutaneous drain, antibiotics)
- Success rate of intervention and overall
- Stoma reversal rate
- Length of stay
- 30 day mortality rate

Report the numbers of published studies included and excluded at each stage in an appropriate format (e.g. PRISMA flow diagram).



Current Anastomotic Leak Outcome

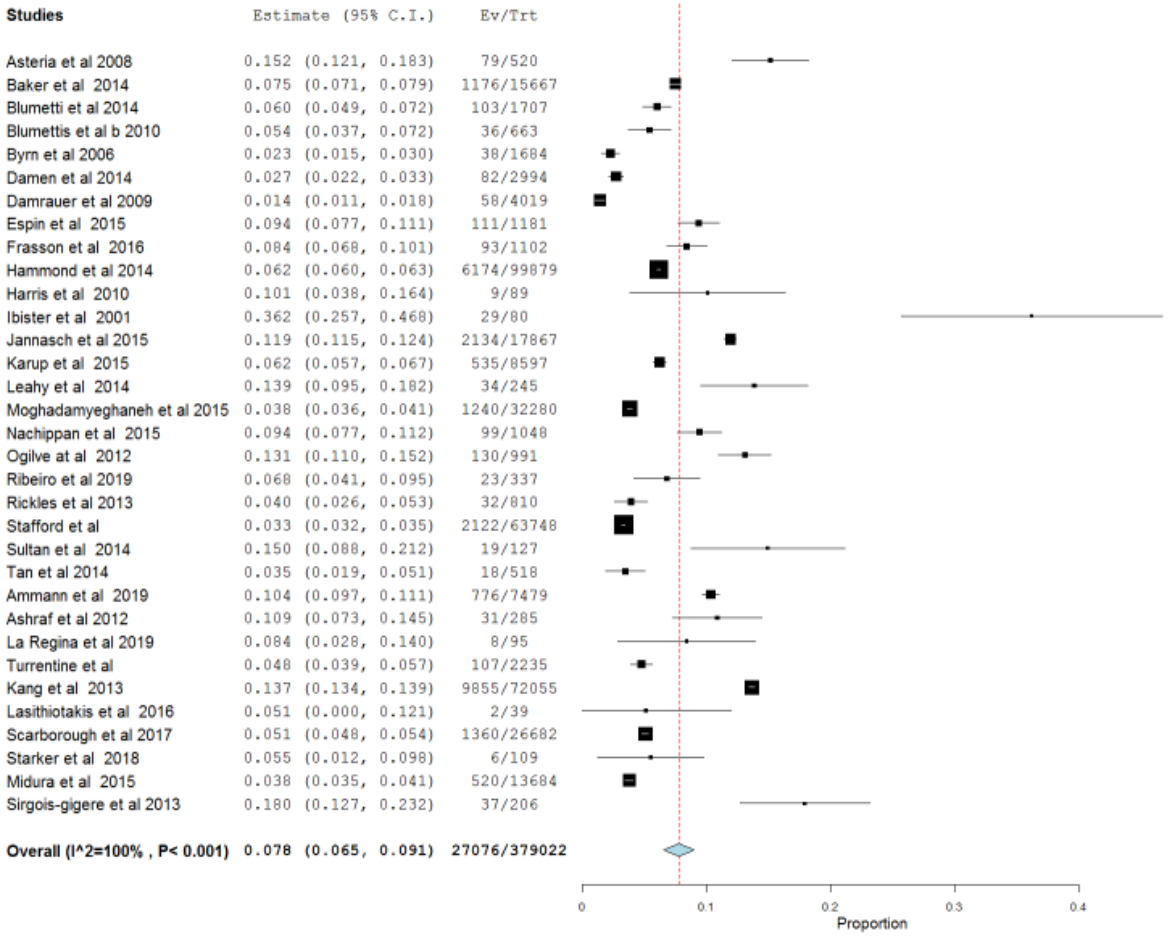
List any relevant studies below.

Study Author	Study Title
(Asteria et al. 2008)	Anastomotic leaks after anterior resection for mid and low rectal cancer: survey of the Italian Society of Colorectal Surgery
(Bakker et al. 2014)	Risk factors for anastomotic leakage and leak-related mortality after colonic cancer surgery in a nationwide audit
(Blumetti et al. 2014)	Management of anastomotic leak: lessons learned from a large colon and rectal surgery training program
(Blumetti et al. 2012)	Delayed transanal repair of persistent coloanal anastomotic leak in diverted patients after resection for rectal cancer
(Byrn et al. 2006)	The management of 38 anastomotic leaks after 1,684 intestinal resections
(Choudhuri and Uppal 2013)	Predictors of septic shock following anastomotic leak after major gastrointestinal surgery: An audit from a tertiary care institute
(Damen et al. 2014)	Anastomotic leaks in colorectal surgery
(Damrauer, Bordeianou, and Berger 2009)	Contained anastomotic leaks after colorectal surgery: are we too slow to act
(Espin et al. 2015)	Oncological outcome following anastomotic leak in rectal surgery.
(Felder et al. 2014)	Risk factors for failure of percutaneous drainage and need for reoperation following symptomatic gastrointestinal anastomotic leak
(Frasson et al. 2016)	Risk factors for anastomotic leak and postoperative morbidity and mortality after elective right colectomy for cancer: results from a prospective, multicentric study of 1102 patients
(Hammond et al. 2014)	The burden of gastrointestinal anastomotic leaks: an evaluation of clinical and economic outcomes
(Harris et al. 2010)	Outcomes of low anterior resection anastomotic leak after preoperative chemoradiation therapy for rectal cancer
(Isbister 2001)	Anastomotic leak in colorectal surgery: A single surgeon's experience
(Jannasch et al. 2015)	Risk factors, short and long term outcome of anastomotic leaks in rectal cancer
(Khan et al. 2008)	The management and outcome of anastomotic leaks in colorectal surgery
(Krarup et al. 2015)	Association of Comorbidity with Anastomotic Leak, 30-day Mortality, and Length of Stay in Elective Surgery for Colonic Cancer: A Nationwide Cohort Study
(Leahy et al. 2014)	What is the risk of clinical anastomotic leak in the diverted colorectal anastomosis
(Midura et al. 2015)	Risk factors and consequences of anastomotic leak after colectomy: a national analysis.
(Moghadamyeghaneh et al. 2016)	Contemporary management of anastomotic leak after colon surgery: assessing the need for reoperation.
(Nachiappan et al. 2015)	The impact of anastomotic leak and its treatment on cancer recurrence and survival following elective colorectal cancer resection
(Ogilvie, Dietz, and Stocchi 2012)	Anastomotic leak after restorative proctosigmoidectomy for cancer: what are the chances of a permanent ostomy?
(Phan et al. 2019)	Does a stoma reduce the risk of anastomotic leak and need for re-operation following low anterior resection for rectal cancer: systematic review and meta-analysis of randomized controlled trials
(Phitayakorn et al. 2008)	Standardized algorithms for management of anastomotic leaks and related abdominal and pelvic abscesses after colorectal surgery
(Ribeiro et al. 2019)	The Clinical and Economic Burden of Colorectal Anastomotic Leaks: Middle-Income Country Perspective
(Rickles et al. 2013)	Anastomotic leak or organ space surgical site infection: What are we missing in our quality improvement programs?

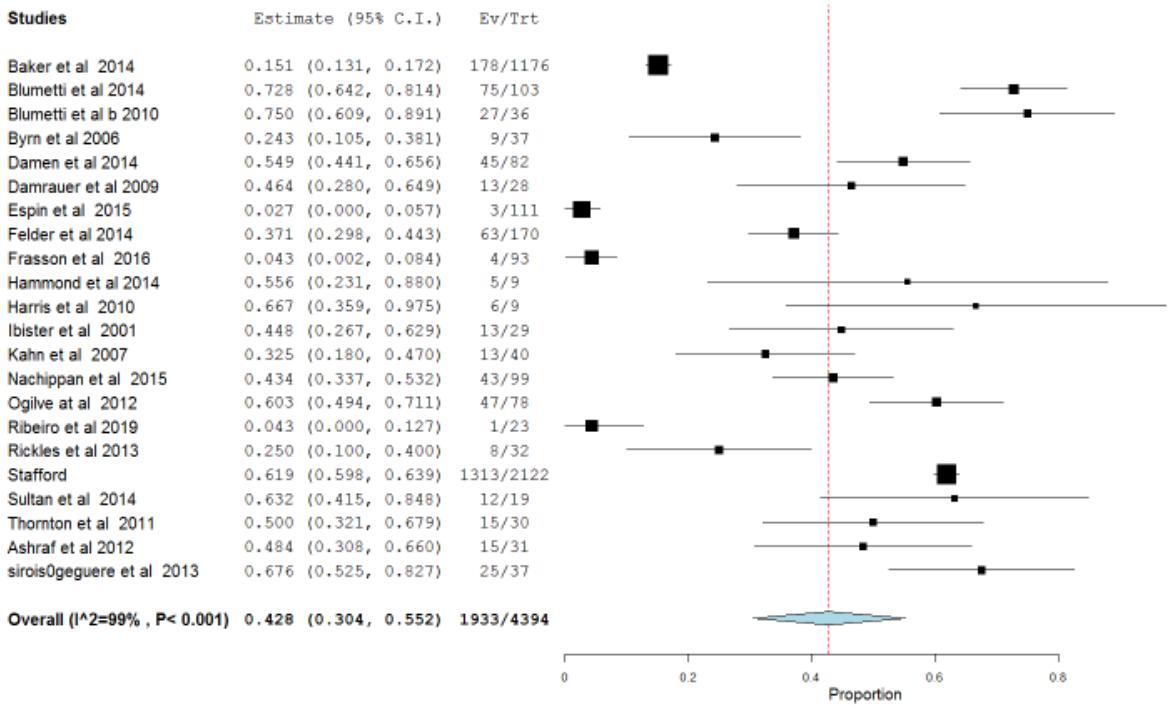
(Schiff et al. 2017)	Diagnosis and Management of Intraoperative Colorectal Anastomotic Leaks: A Global Retrospective Patient Chart Review Study
(Sirois-Giguère et al. 2013)	Transanal drainage to treat anastomotic leaks after low anterior resection for rectal cancer: a valuable option
(Stafford et al. 2018)	Is Diversion with Ileostomy Non-inferior to Hartmann Resection for Left-sided Colorectal Anastomotic Leak?
(Sultan, Chawla, and Zaidi 2014)	Factors affecting anastomotic leak after colorectal anastomosis in patients without protective stoma in tertiary care hospital
(Tan et al. 2014)	Anastomotic leaks after colorectal anastomosis occurring more than 30 days postoperatively: a single-institution evaluation.
(Thornton et al. 2011)	Management and outcome of colorectal anastomotic leaks.

Meta-analysis Current therapies

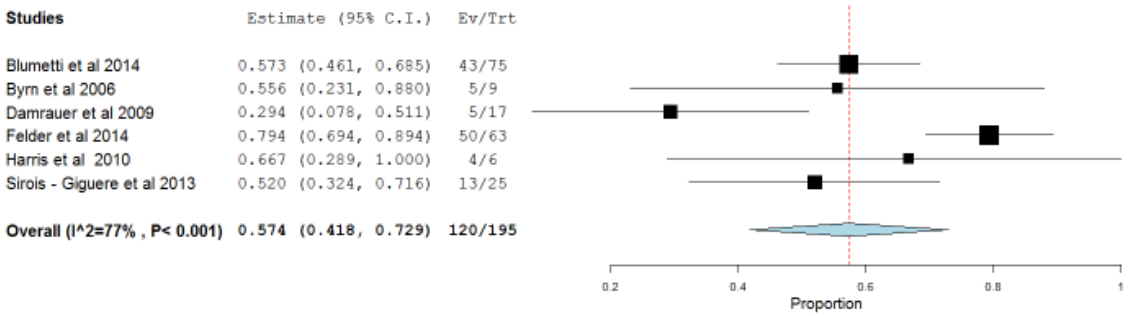
In total 379,022 patients with an anastomosis were included in the analysis with 27,076patients resulting in an anastomotic leak (AL). Binary regression demonstrated a weighted mean rate of occurrence of AL of 7.8% (95% CI 6.5 to 9.1%) (I^2 = 100%).



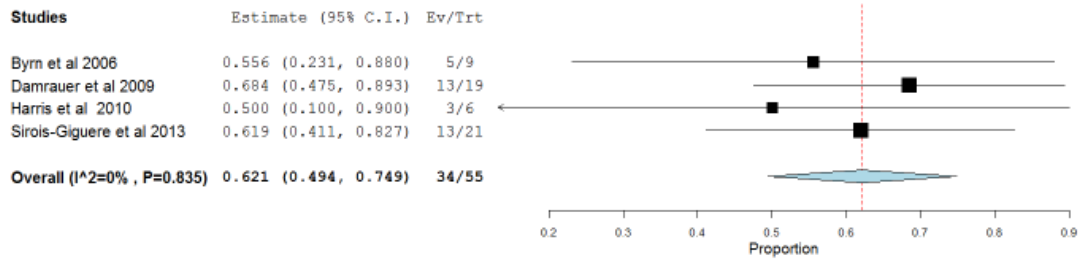
Currently out of 1933/4394 (44.0%) AL are treated by non-operative means. Binary regression demonstrated a weighted mean rate of non-operative treatment of AL of 42.8% (95% CI 30.4 to 55.2%) (I^2 = 99%).



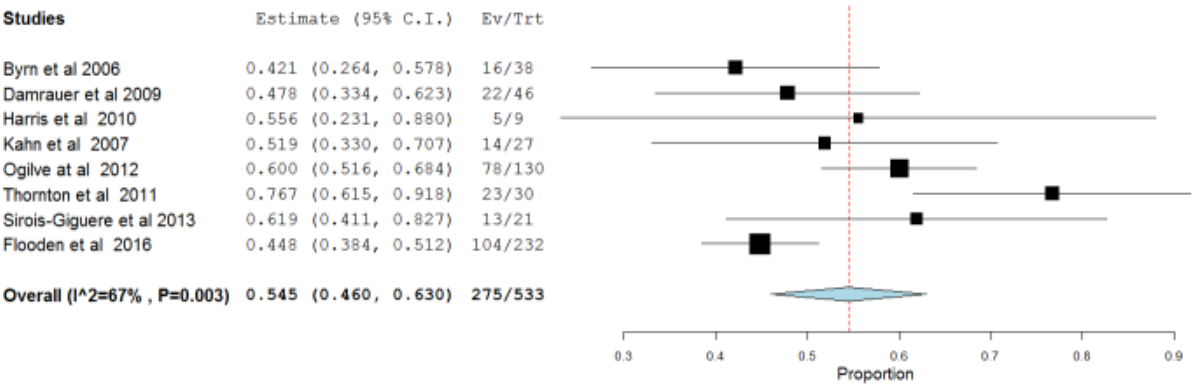
Non operative success rate was available from 6 studies covering 195 patients. From these studies 120/195 (60.82%). Binary regression demonstrated a weighted mean rate of non-operative successful healing of AL currently of 57.4% (95% CI 41.8 to 72.9%) (I^2 = 77%).



Stoma reversal rate following non operative treatment was discussed in 4 studies with 34/551 (61.8%) patients successfully having their stoma reversed following non-operative treatment. Binary regression demonstrated a weighted mean rate of non-operative stoma reversal at 62.1% (95% CI 49.4 to 74.9%) (I^2 = 55%).

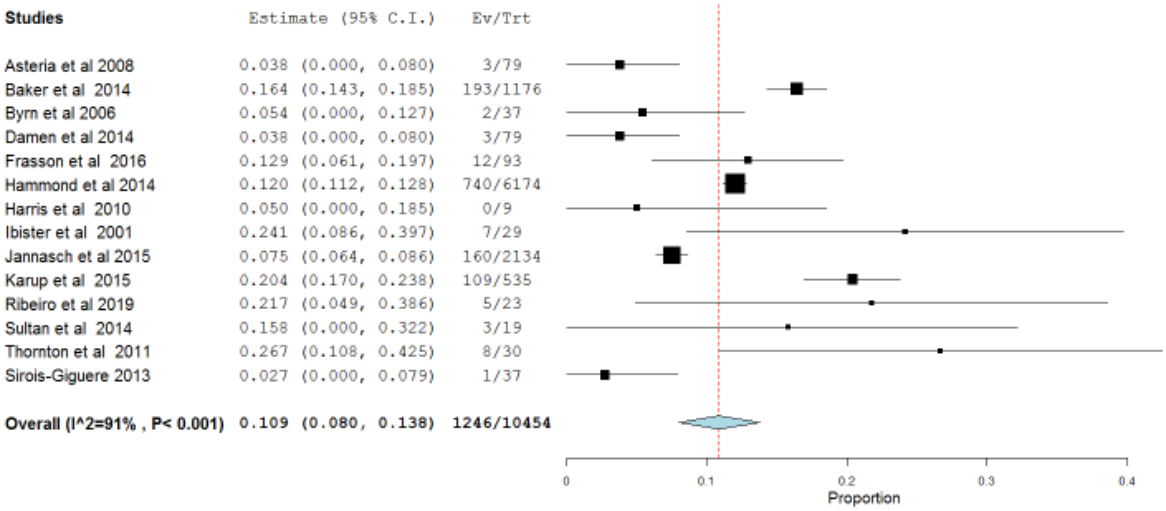


Due to the small number of studies and patients covering current stoma reversal following non-operative treatment of AL, all current treatments for AL were analysed with regards to stoma reversal rate. Eight studies covered stoma reversal, with 275/533 (51.6%) patients successfully having their stoma reversed after an AL. Binary regression demonstrated a weighted mean rate for stoma reversal of 54.5% (95% CI 46.0 to 63.0%) (I^2 = 68%).

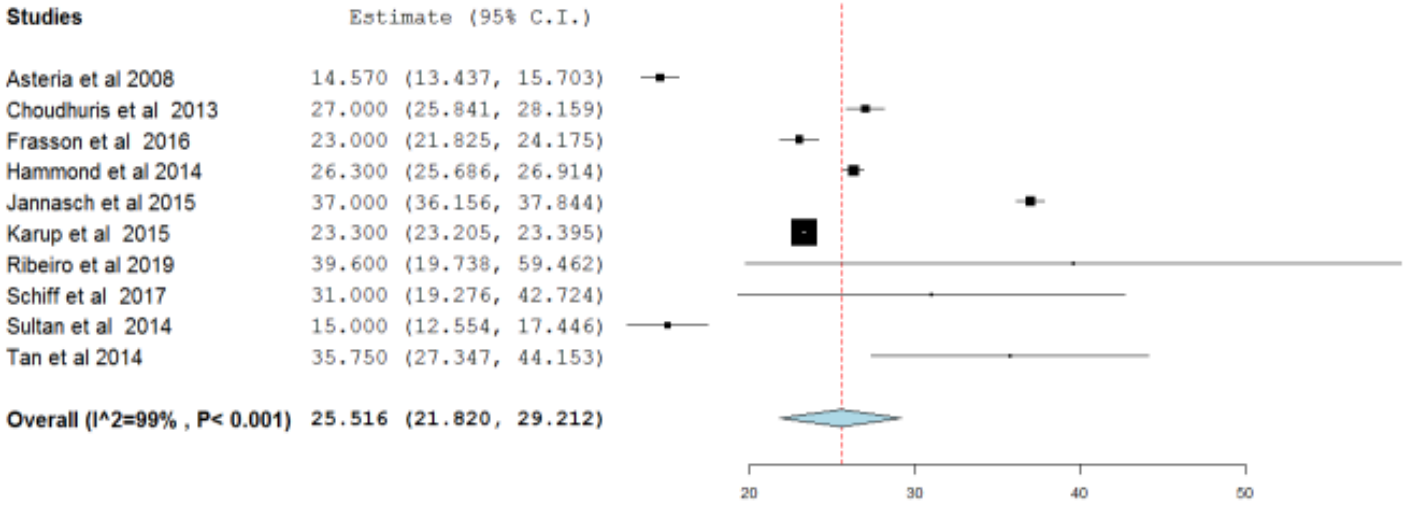


Current 30 day mortality following AL with all current treatment was covered in 14 papers with 1246/10,454 (11.9%) patients having 30 d mortality following AL. Binary regression demonstrated a weighted mean rate

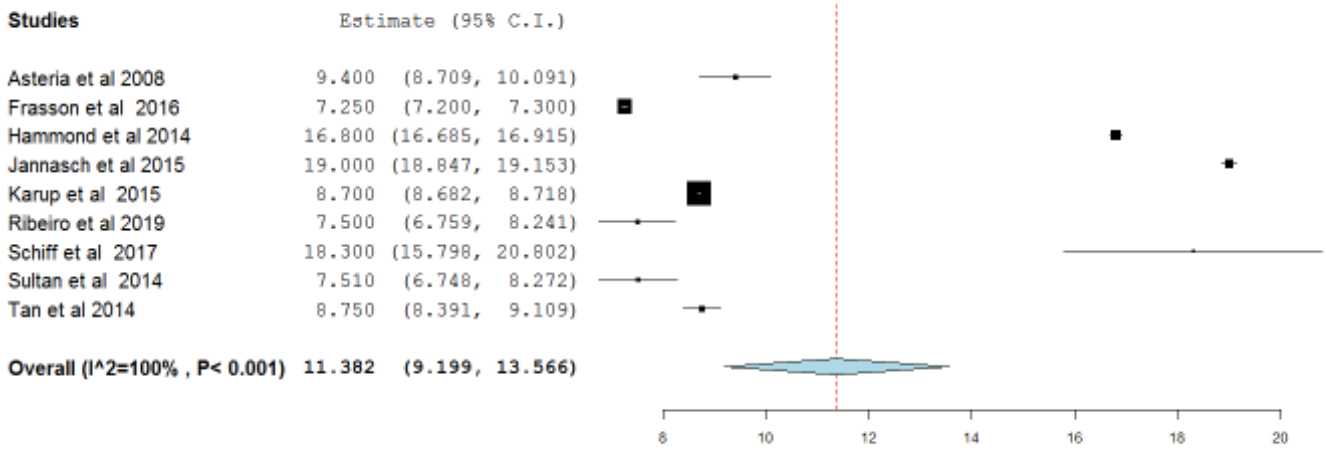
for 30 day mortality of 10.9% (95% CI 8.0 to 13.8%) (I^2 = 91%). Weighted mean could not be identified for non–operative treatment alone.



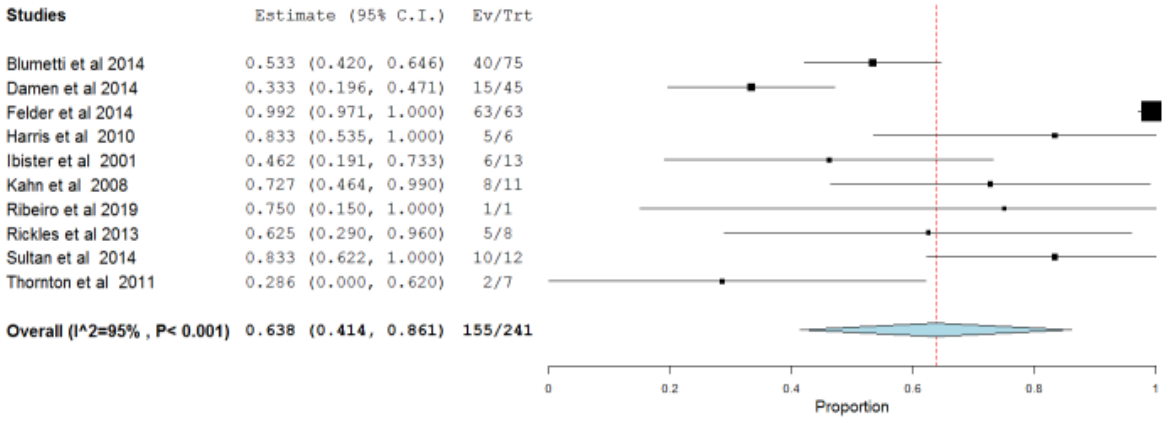
Current length of stay (LOS) following AL was reported in 10 journal articles. Continuous regression demonstrated a weighted mean LOS with AL of 25.15 days (95% CI 21.82 to 29.21 days) (I^2 = 99%).



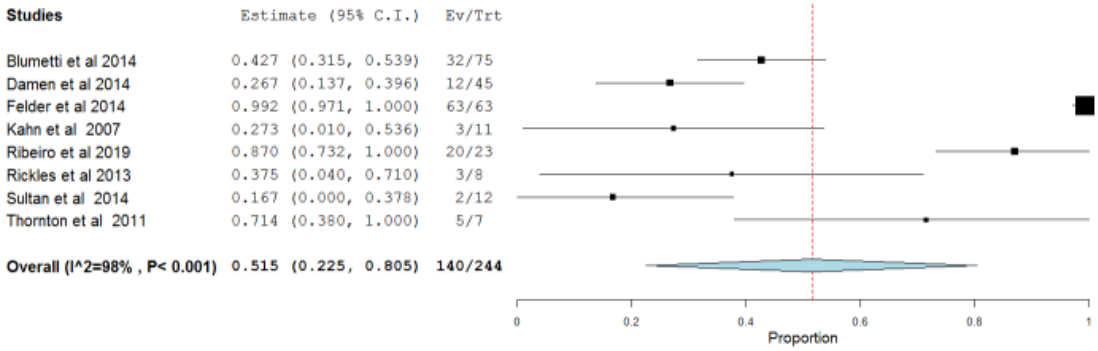
Current length of stay without AL was also analysed with continuous regression demonstrating a weighted mean without AL of 11.38 days (95% CI 9.20 to 13.56 days) (I^2 = 99%).



Of patients treated with a non-operative route 155/241 (64.3%) were treated with percutaneous drain. Binary regression demonstrated a weighted mean rate of percutaneous drain treatment (within non-operative group) of 62.8% (95% CI 36.9 to 88.7%) (I^2 = 97%).



Of patients treated with a non-operative route 140/244 (57.4%) were treated with antibiotics. Binary regression demonstrated a weighted mean rate of antibiotic treatment (within non-operative group) of 51.5% (95% CI 22.5 to 80.5%) (I^2 = 98%).



Time to stoma reversal was covered in only two studies. Mean time to healing was reported as 10.6 (95% CI 7.55 to 13.62 months) by Harris et al and 10.23 months (95% CI 8.36 to 12.89 months) by Khan et al, (Harris et al. 2010; Khan et al. 2008).

Appendix C: Search strategy for adverse events

Date search conducted:	5.9.19
Date span of search:	Conception to 5.9.19

List the complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean). List the databases that were searched.

Set#	Searched for TX	Results		
		CINAHL Complete, Medline Complete, Biomedical Reference Collection and STM	**Cochrane Library**	**Pubmed**
S1	Endo-SPONGE	162	1	25
S2	Endo-SPONGE	154	2	20
S3	Endoscopic vacuum therapy	3,829	8	337
S4	Endoscopic vacuum-assisted	1,181	10	89
S5	Transanal vacuum therapy	278	1	10
S6	ETVARD	18	0	2
S7	S1 OR S2 OR S4 OR S4 OR S5 OR S6 6	4,159	13	381
S8	Rectum	296,886	-	73,827
S9	Colorectal	750,866	-	165,477
S10	Rectal	428,841	-	114,688
S11	anorectal	40,733	-	11,163
S12	S8 OR S9 OR S10 OR S11	1,152,925	-	287,097
S13	Anastomotic leak	31,530	-	6261
S14	S7 And S12 AND S13	605	13	32
S14	S14 NOT eosophagus	257		

Total = 302

Brief details of any additional searches, such as searches of company or professional organisation databases (include a description of each database):

Previous company search Date: 24th December 2018 and 2nd January 2019
EMBASE and Google Scholar Endo-SPONGE or Endo-SPONGE
Limitations:

- Time period: 2012 – January 2019
- English and Spanish language

Papers not already included in initial search n= 13. These papers were included at stage for full paper analysis

Inclusion and exclusion criteria:	
Inclusion criteria	
Population	Lower gastrointestinal tract anastomotic leaks.
Interventions	Endo-SPONGE alone.
Outcomes	Success of stopping leak and time taken. Closure of protective stoma and time taken. Complication rate.
Study design	Systematic reviews, randomised, non-randomised, cohort, observational Case series, Case studies and qualitative studies.
Language restrictions	No language restrictions.
Search dates	5.9.19
Exclusion criteria	
Population	Upper gastrointestinal tract anastomotic leaks
Interventions	Endo-SPONGE in conjunction with other interventions (early surgical closure, over scope clips etc.). Any non Endo-SPONGE endoscopic vacuum therapy. Any other intervention other than endoscopic vacuum therapy. Used outside of device instructions for use (e.g. colonoscopy perforation).
Outcomes	
Study design	Testimonials, non-systematic reviews containing no primary data, editorials, reports describing product news. In vitro studies.
Language restrictions	Unable to obtain translation.
Search dates	5.9.19

Data Abstraction

Any complication
Any adverse event reported
Any reference to adverse event not occurring.

Adverse events evidence

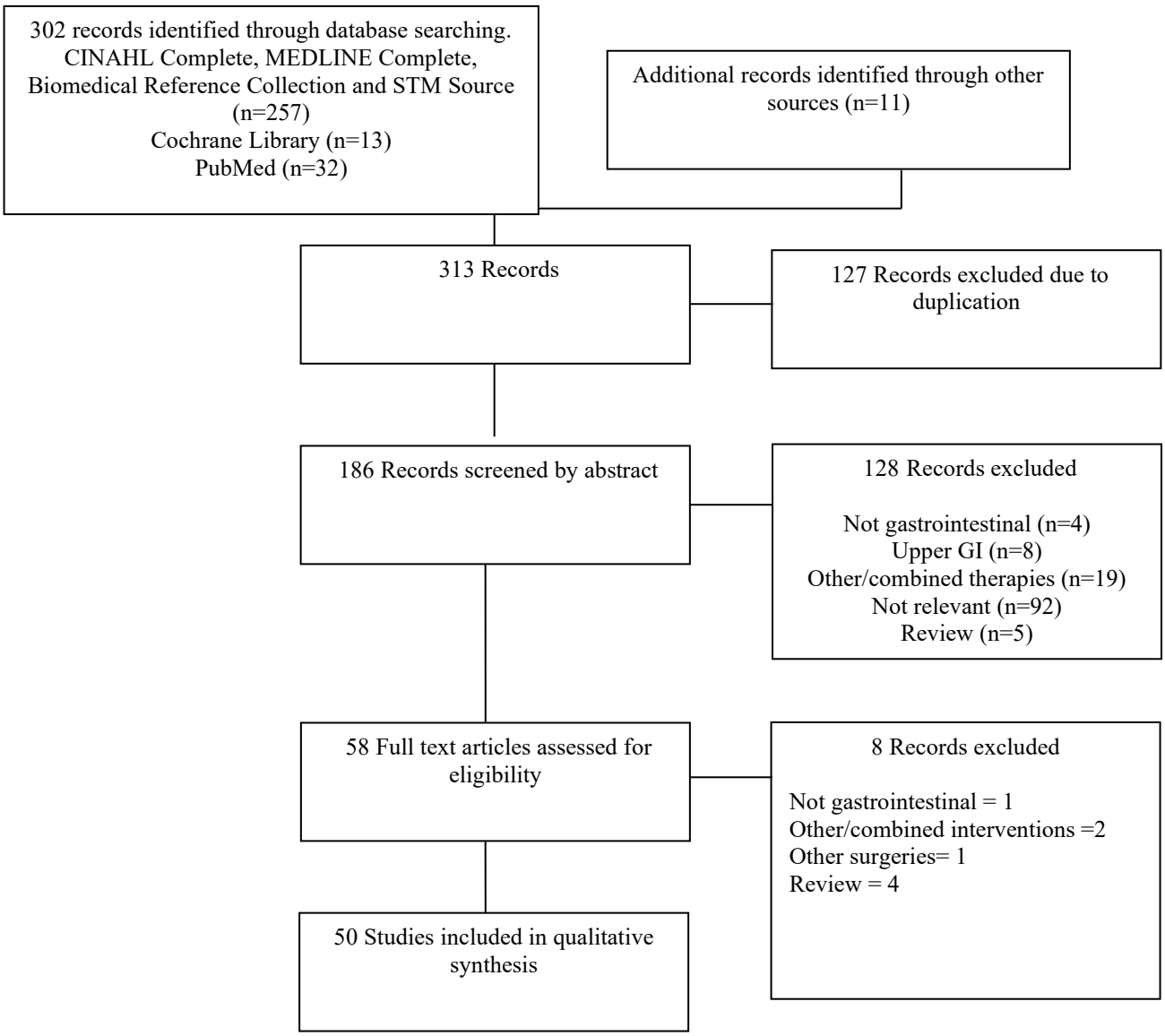
List any relevant studies below. If appropriate, further details on relevant evidence can be added to the adverse events section.

Study	Design and intervention(s)	Details of adverse events	Company comments
Arezzo et al 2015	Endo-SPONGE	0/14 patients experienced complications/adverse events	Text
Boschetti et al 2018	Endo-SPONGE	0/29 complications/ adverse events	Text
Huisman et al 2019	Endo-SPONGE	3/20 chronic sinus	The event is listed in the IFU of Endo-SPONGE.
Jimenez-Rodriguez et al 2018	Endo-SPONGE	22/22 patients experienced discomfort, well tolerated 1/22 anastomotic stenosis 1/22 chronic fistula 1/22 osteomyelitis	Stenosis is main complication of AL management and link to AL. Discomfort, stenosis and fistula are listed in the IFU of Endo-SPONGE. Due to the underlying disease most patients have a localised infection which can lead to further infection
Keskin et al, 2015	Endo-SPONGE	2/15 sepsis 1/15 bleeding	Due to the underlying disease most patients have a localised infection which can lead to further infection Bleeding is an event is listed in the IFU of Endo-SPONGE.
Knuth et al 2016	Endo-SPONGE	0/1 complication/ adverse events	Pain is listed in the IFU of Endo-SPONGE.
Martinotti et al 2014	Endo-SPONGE	0/4 complication/ adverse events	Text
Milito et al 2017	Endo-SPONGE	5/14 mild pain	Pain is listed in the IFU of Endo-SPONGE.
Mussettos et al 2017	Endo-SPONGE	2/11 anastomotic stricture	Stenosis is main complication of AL management ad link to AL and is and event is listed in the IFU of Endo-SPONGE.
Nerup et al, 2013	Endo-SPONGE	1/13 stenosis	Stenosis is main complication of AL management ad link to AL and is and event is listed in the IFU of Endo-SPONGE.

Riss et al, 2009	Endo-SPONGE	0/6 complications/ adverse events	
Riss et al, 2010	Endo-SPONGE	1/23 stenosis 5/23 recurrent abscess	Stenosis is main complication of AL management ad link to AL and is and event is listed in the IFU of Endo-SPONGE. Due to the underlying disease most patients have a localised infection which can lead to further infection. Abscess is an event is listed in the IFU of Endo-SPONGE.
Srinivasamurthy et al	Endo-SPONGE	1/8 pain, 1/8 inadvertent placement 1/8 fistula	Pain and fistula formation are events listed in the IFU of Endo-SPONGE.
Strangio et al, 2015	Endo-SPONGE	1/25 urethirc fistula 1/25 ileal fistula 1/25 para-rectal abscess	Fistula is an events listed in the IFU of Endo-SPONGE. Due to the underlying disease most patients have a localised infection which can lead to further infection. Abscess is an event is listed in the IFU of Endo-SPONGE.
Van Koperen et al, 2009	Endo-SPONGE	1/16 bleeding 500 cc 1/16 pain stopped therapy 1/16 stopped due to near complete dehiscent anastomosis 1/16 recurrent abscess.	Pain, bleeding and abscess are events listed in the IFU of Endo-SPONGE.
Weidenhagen et al, 2008	Endo-SPONGE	0/34 pain, 0/34 major bleeding. Minor bleeding mentioned without details of frequency 2/34 ischemic necrosis 1/34 rectovaginal fistula	Pain, bleeding and fistula are events listed in the IFU of Endo-SPONGE.
Wood et al 2015	Endo-SPONGE	N=1 case of fungal endophthalmitis	The authors claim that theirs is the first report case where the use of Endo-SPONGE has been associated with disseminated fungal infection resulting in haematogenous spread to the eyes.

Report the numbers of published studies included and excluded at each stage in an appropriate format (e.g. PRISMA flow diagram).

Response



Structured abstracts for unpublished studies

Study title and authors
Introduction
Objectives
Methods
Results
Conclusion
Article status and expected publication: Provide details of journal and anticipated publication date

No Unpublished studies

Appendix C: Checklist of confidential information

Please see section 1 of the user guide for instructions on how to complete this section.

Does your submission of evidence contain any confidential information? (please check appropriate box):

No ☒ If no, please proceed to declaration (below)

Yes ☐ If yes, please complete the table below (insert or delete rows as necessary). Ensure that all relevant sections of your submission of evidence are clearly highlighted and underlined in your submission document, and match the information in the table. Please add the referenced confidential content (text, graphs, figures, illustrations, etc.) to which this applies.

Page	Nature of confidential information	Rationale for confidential status	Timeframe of confidentiality restriction
#	☐ Commercial in confidence ☐ Academic in confidence	Enter text.	Enter text.
Details	Enter text.		
#	☐ Commercial in confidence ☐ Academic in confidence	Enter text.	Enter text.
Details	Enter text.		

Confidential information declaration

I confirm that:

- all relevant data pertinent to the development of medical technology guidance (MTG) has been disclosed to NICE
- all confidential sections in the submission have been marked correctly
- if I have attached any publication or other information in support of this notification, I have obtained the appropriate permission or paid the appropriate copyright fee to enable my organisation to share this publication or information with NICE.

Please note that NICE does not accept any responsibility for the disclosure of confidential information through publication of documentation on our website that has not been correctly marked. If a completed checklist is not included then NICE will consider all information contained in your submission of evidence as not confidential.

Signed*: ** Must be Medical Director or equivalent*		**Date:**	January 2, 2020
Print:	Dr. Ricard Rosique Gastrointestinal Surgeon	**Role / organisation:**	Head Medical Scientific Affairs B. Braun Group Spain
Contact email:	ricard.rosique@bbraun.com		

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technologies guidance

MT461 – Endo-SPONGE for colorectal anastomotic leakages

Company evidence submission

Part 2: Economic evidence

Company name	B Braun Medical Ltd
Submission date	Click or tap here to enter date.
Contains confidential information	Yes / No

Contents

1 Published and unpublished economic evidence

Identification and selection of studies

Complete the following information about the number of studies identified.

Please provide a detailed description of the search strategy used, and a detailed list of any excluded studies, in appendix A and B.

Due to a lack of comparative studies using Endo-SPONGE and hence a lack of economic studies for Endo-SPONGE, the outcome of AL treatment with a resource impact have been systematically searched for both Endo-SPONGE and where possible, for the current AL pathway.

Outcomes for Endo-SPONGE

Number of studies identified in a systematic search.		313
Number of studies identified as being relevant to the decision problem.		51 (21 after exclusions)
Of the relevant studies identified:	50 (20 after exclusions)	51 (21 after exclusions)
	Number of abstracts.	0
	Number of ongoing studies.	0

Outcomes for Current AL pathways

Number of studies identified in a systematic search.		317
Number of studies identified as being relevant to the decision problem.		37
Of the relevant studies identified:	Number of published studies.	37
	Number of abstracts.	0
	Number of ongoing studies.	0

List of relevant studies

In table 1, provide brief details of any published or unpublished economic studies or abstracts identified as being relevant to the decision problem. No economic studies for Endo-SPONGE have been identified.

For any unpublished studies, please provide a structured abstract in appendix A. If a structured abstract is not available, you must provide a statement from the authors to verify the data provided.

Any data that is submitted in confidence must be correctly highlighted. Please see section 1 of the user guide for how to highlight confidential information. Include any confidential information in appendix E.

Table 1a list published studies for Endo-SPONGE with regards to outcome and resource, table 1b list published studies for current AL pathway with regards to outcome and resource.

Table 1 Summary of all relevant studies For Outcomes Endo-SPONGE (published and unpublished)

Author, year and location	Patient population,	Intervention	Comparator(s)	Main outcomes
(Arezzo et al. 2015b), Italy	Patients following colorectal leaks treated with endoscopic vacuum therapy.	Endo-SPONGE	None	79% successful leak closure. Median duration of treatment was 12.5 sessions (range 4–40). Median time for complete healing was 40.5 days (range 8–114), for a median cost of treatment of 3125 Euros.
(Boschetti G 2018) France	Patients with clinical symptomatic anastomotic leak treated by Endo-SPONGE.	Endo-SPONGE	None	Closure in 93% of patients, maintained in 89% of patients after 6 months. Mean 18.6 ± 13 Endo-SPONGE session required. 87.5 % Stoma reversal rate.
(Clifford et al. 2019)	Patients with anastomotic leaks following colorectal surgery.	Endo-SPONGE	Stent, endoscopic clips, endoscopic drainage, fibrin glue	Successful leak closure for vacuum assisted closure 88.8% (range 66.6-100%).
(Huisman et al. 2019) Netherlands	Symptomatic anastomotic leakage after rectal surgery treated with Endo-SPONGE.	Endo-SPONGE	None	Successful leak closure 85%, bowel continuity restored 70%. 79% stoma reversal rate.
(Jimenez-Rodriguez et al. 2018) Spain	Patients with dehiscence of lower colorectal anastomosis or opening of the rectal stump after anterior resection for rectal cancer.	Endo-SPONGE	None	Full resolution 86%. Mean time to healing 22.3 ±14.7 days. Mean number of endoscopy sessions 3.1± 1.9. 39% stoma reversal rate.
(Katz et al. 2018) Israel	Patients with leaking colorectal anastomosis.	Endo-SPONGE	None	Successful leak closure for 100%. Regained bowel continuity 85%. Stoma closure in 80%. Mean number of sponge exchanges 3.6 (range 3-5). 80% stoma reversal rate.
(Keskin et al. 2015) Turkey	Patients with anastomotic leak and cavity formation following colorectal surgery.	Endo-SPONGE	None	Successful leak closure 80%. Mean 2.2 sponge exchanges (range 1-5). Lumen integrity achieved 67%. 71% stoma reversal rate.
(Kuehn et al. 2016) Germany	Patients with use of endoscopic vacuum therapy for various lower gastrointestinal tract defects.	Endo-SPONGE	None	Anastomotic leak closure 90%, average number of sponges used 7 (range 1-37). 79% stoma reversal rate.
(Manta et al. 2016) Italy	Patients with different post-surgical leaks involving the gastrointestinal tract managed with endoscopy as initial approach.	Endo-SPONGE	Over-the-scope clip. Self-expanding metal stent. Fibrin glue injection.	Successful closure with Endo-SPONGE 100%.

(Milito et al. 2017) Italy	Patients with anastomotic leak and cavity formation following colorectal surgery.	Endo-SPONGE + antibiotics	None	Well tolerated with no complications
(Mussetto et al. 2017) Italy	Patients with anastomotic leaks following colorectal surgery.	Endo-SPONGE	None	Anastomotic leak closure 90%, mean 19 sponge changes (range 9-23). All patients with healed leak had ileostomy closed.
(Nerup et al. 2013) Denmark	Patients with anastomotic leak following low anterior resection of rectal cancer.	Endo-SPONGE	None	Anastomotic leak closure 100%. Stoma closure 92%. Median number of treatments 8 (range 1-18).
(Popivanov et al. 2019)	Patients receiving endoluminal negative pressure therapy in colorectal anastomotic leaks.	Endo-SPONGE and non Endo-SPONGE	None	Successful closure 85.4%. Stoma closure 72.6%. Median 7 sponge exchanges (range 2-34).
(Riss et al. 2009) Austria	Patients following surgery for low rectal cancer suffering an anastomotic leak following anterior rectal resection or leak of rectal stump following Hartmann's procedure.	Endo-SPONGE	None	Successful leak closure 66.6%.
(Riss et al. 2010) Austria	Patients who had undergone initially successful Endo-SPONGE assisted treatment of anastomotic leakage following rectal cancer surgery were included in the study.	Endo-SPONGE	None	Long term success after leak closed initially 75%. 87% AL closure rate and 77% stoma reversal rate.
(Rottoli et al. 2018) Italy	Patients with diagnosed anastomotic leak following IPAA (ileal pouch-anal anastomosis).	Endo-SPONGE	None	100% healing of leak, 88% ileostomy reversal.
(Shalaby et al. 2019) 2019	Patients treated with endoluminal vacuum assisted therapy for colorectal anastomotic leakage.	Endo-SPONGE and non Endo-SPONGE	None	Successful leak closure rate 82.6%. Following successful treatment 75.9% had stoma reversed. Complication rate 13.8%.
(Srinivasamurthy et al. 2013b) UK	Patients with low pelvic anastomotic leakage (n=7 low anterior resection for colorectal cancer, n=1 restorative proctocolectomy for ulcerative colitis).	Endo-SPONGE	None	Complete closure or significant reduction in size of abscess 75%. Stomas reversed and good function 63%. Mean 4 sponge application (range 1-7).
(Strangio et al. 2015) Italy	Patients with anastomotic leakage following colorectal surgery, mixed reasons for surgery.	Endo-SPONGE	None	Successful leak closure 88%, complication rate 12%. Median 9 applications (range 1-39).

(Van Koperen et al. 2008) Netherlands	Patients with anastomotic leak following low anterior resections for rectal cancer or restorative proctocolectomy with ileoanal pouch anastomosis for ulcerative colitis.	Endo-SPONGE	None	Cavity closure rate 56%. 56% stoma reversal
(Weidenhagen et al. 2008) Germany	Patients with anastomotic leakages after anterior resection.	Endo-SPONGE	None	Anastomotic leak healing achieved 97%, stoma closure rate 88%. Number of Endo-SPONGE applications 11 (range 1-27).

Table 1b Summary of all relevant studies For Outcomes Current AL Pathway (published and unpublished)

Author, year and location	Patient population,	Current treatments	Main outcomes
(Asteria et al. 2008)	Patients with mid or low rectal cancer who underwent sphincter saving surgery	Not detailed	The overall incidence of AL was 15.2% (79 of 520), and 12 (2.3%) patients died within 30 days of surgery including 3 patients (0.58%) with AL. Of the 79 patients with AL, 32 (40.5%) were grade 1, 26 (32.9%) were grade 2, 17 (21.5%) were grade 3, and 4 (5.1%) were grade 4. The mean hospital stay was 12.04 days (SD 6.29). Among the 79 patients with AL, the mean hospital stay was of 14.57 days (SD 5.14) which was significantly higher than the hospital stay of patients without AL (9.433±7.440 days; *p*<0.003). 30 day mortality n=3/79 (3.8%).
(Bakker et al. 2014)	Patients undergoing surgical resection for colorectal cancer with creation of an anastomosis	Laparotomy, laparoscopy, radiological drainage, other drainage.	AL leading to re-intervention occurred in 1176 patients (7·5%). The re-interventions were laparotomy (82·1%), laparoscopy (2·8%), radiological drainage (8·2%), and interventions such as drainage of wounds and abscesses (6·9%). The mortality rate among patients with AL was 16·4%. A secondary stoma was created in 805 patients (68·5%) requiring a surgical or radiological re-intervention for AL.
(Blumetti et al. 2014)	Patients having received bowel resection and anastomosis formation.	Operative and non-operative	There were 103 leaks identified in 1,707 bowel anastomoses (6 %). Leaks were diagnosed at a median time of 20 days postoperatively (range 2–1400 days). There were three deaths resulting from the anastomotic leak (90-day mortality 3 %). In all, 75 % of patients (75/103) with anastomotic leak were managed non-operatively, and 27 % (28/103) were managed operatively. The success rate was 54 % for operative management and 57 % for non-operative management (p = 0.73), with an overall success rate of 56 %. Percutaneous drainage was performed in 40/75 (53.3%), patients treated non-operatively. Antibiotics were given to 32/75 (42.7%) patient treated non-operatively part of their treatment
(Blumetti et al. 2012)	Patients receiving low anterior resections	Operative and non-operative	AL occurred in 36/663 (5.4%) low anterior resections. Non-operative treatment occurred in n=27/36 (75%) of AL.
(Byrn et al. 2006)	Patients following small bowel and large bowel surgery	Operative and non-operative	AL occurred in 38/1684 (2.3%) of surgeries. Percutaneous drainage was used in n=9 patients. N=9 patients treated non-operatively, n=5/9 non-operative success rate. N=5/9 stoma reversal rate for non-operative pathway and n=16/38 stoma reversal rate overall.
(Choudhuri and Uppal 2013)	Patients with anastomotic leak admitted into ICU following major gastrointestinal surgery		103 AL, n=90/103 sepsis and 72/103 septic shock.

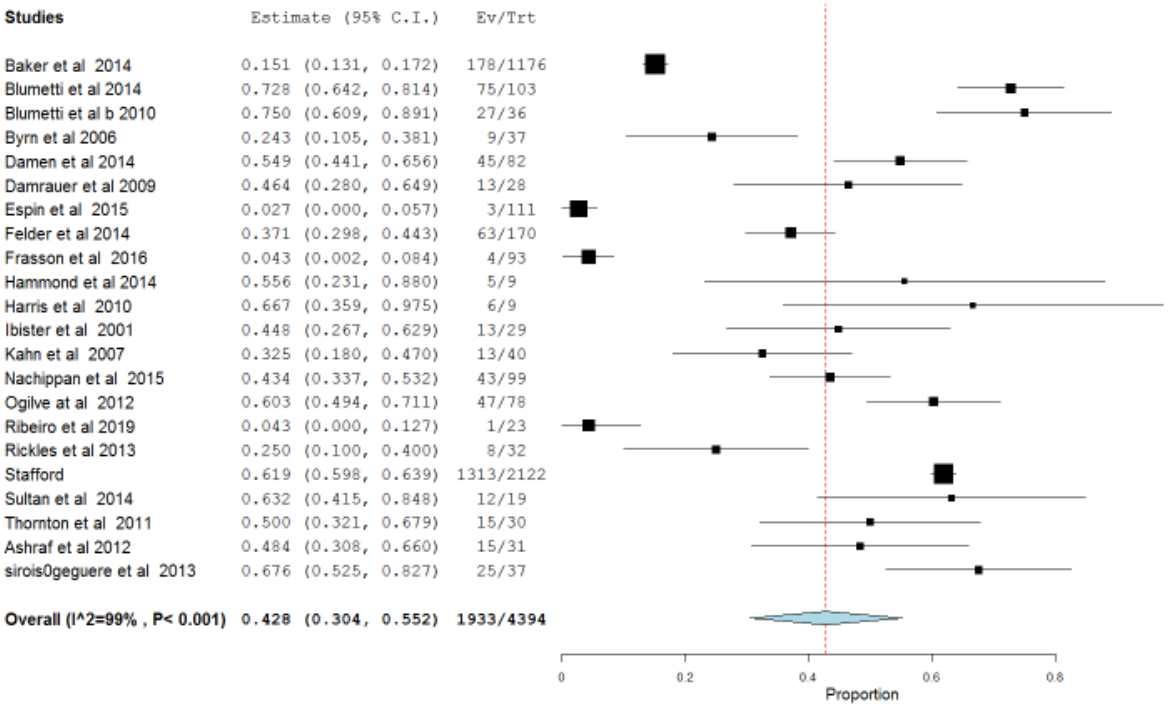
(Damen et al. 2014)	Patients undergoing large/small intestinal resections for benign or malignant disease	Operative and non-operative	AL rate 82/2994 (2.7%). Non-operative treatment used in 45/82 AL (54.9%). 30 day mortality 3/79 patients. Percutaneous drain used to treat 15/45 AL (33.3%). Antibiotics were used for 12/45 (26.7%) of leaks treated non-operatively
(Damrauer, Bordeianou, and Berger 2009)	Patients who underwent colectomy with primary anastomosis	Operative and non-operative	AL rate 58/4019 (1.4%). Non-operative treatment used in 13/28 contained leaks (46.4%) of leaks. Overall non-operative success rate 5/17 (29.4%). Stoma reversal of contained leaks n=13/19 (68.4%) stoma. Overall stoma reversal rate 22/46 (47.8%).
(Espin et al. 2015)	Patients with tumour < 15cm who underwent low anterior resection.	Operative and non-operative	AL 111/1181 (9.4%) AL. Non-operative treatment provided for n=3/111 (2.7%) patients.
(Felder et al. 2014)	Patients with AL following gastrointestinal surgery	Operative and non-operative	Non-operative treatment for AL n=63/170 37.1%. Non-operative success rate n=50/63 (79.4%). All non-operative treatment were percutaneous drain n=63/63 and all n=63/63 non-operative patients were treated with antibiotics alongside percutaneous drain.
(Frasson et al. 2016)	Patients with elective right colectomy.		AL rate of 93/1102 (8.4%), of which n=4/93 were treated non-operatively (4%). 30 day mortality was 12/93 (12.9%). Median length of stay 23 days with AL and 7.25 without AL.
(Hammond et al. 2014)	Patients who underwent colorectal surgery		AL rate 6174/99879 (6.2%). Post-operative infection in 27 and 9% of patients with and without AL. n=5/9 (55.6%) patient treated with non-operative route. 30 day mortality n=740/6174 (12%). Patients with anastomotic leaks had 0.8 times (P<0.001) higher total costs (of index hospitalisation and re-admission) than patients without leaks.
(Harris et al. 2010)	Patients following low anterior resection	Operative and non-operative	AL rate 9/89 (10.1%). Non-operative treatment of AL n=6/9 (66%). Non-operative success rate 4/6 (66.7%). Non-operative stoma reversal rate n=3/6 (50%), overall stoma reversal rate n=5/9 (55.6%). Mortality rate n=0/9. Of the non-operative treatment n=5/6 (83.3%) patients were treated with percutaneous drainage. Secondary surgery was required following percutaneous drainage for 2/5 (40%) of patients
(Isbister 2001)	Patients treated with surgery by colorectal service	Operative and non-operative	AL rate 29/80 (36.2%). Mortality rate of 24.1% in AL group, compared with 1.7% of no AL group. Stoma closure rate of n=12/14 overall (85.7%). N=13/29 non-operative treatment (44.8%), of the non-operative treatments n=6/13 (46.2%) treated with percutaneous drain.
(Jannasch et al. 2015)	Patients undergone colorectal surgery for rectal carcinoma		AL rate 2134/17867 (11.9%). 30 day mortality 160/2134 (7.5%). Length of stay with AL 37 days, without AL 19 days.
(Khan et al. 2008)	Patients with anastomosis following colorectal surgery	Operative and non-operative	Non-operative treatment rate n=13/40 (32.5%). Overall stoma reversal rate n=14/27 (51.9%). N=3 (7.3%) treated with antibiotics and n=8 (19.5%) treated with drainage.
(Krarup et al. 2015)	Patients following colorectal surgery and anastomosis creation		AL rate 535/8597 (6.2%). 30 day mortality 109/535 (20.4%). Length of stay with AL 23.3 days, without AL 8.7 days.

(Leahy et al. 2014)	Patients with colorectal anastomosis		AL rate 34/245 (13.9%)
(Midura et al. 2015)	Patients following Segmental colectomy with anastomosis		AL rate n=520/13684 (3.8%)
(Moghadamyeghaneh et al. 2016)	Patients following colon resection surgery	Operative and non-operative	AL rate 1240/32280 (3.8%).Non-operative treatment n=544/1240 (43.9%). Of the non-operative treatment n=240/544 (44.1%), were medical intervention n=304/544 (55.9%) were other non-surgical intervention. Among patients with AL, patients who underwent reoperation had significantly higher mortality compared with patients managed with medical treatment or interventional treatments (9.5% vs 6.1%; AOR, 1.98; CI, 1.03 to 3.78; P 5 .03).
(Nachiappan et al. 2015)	Patients following restorative colorectal cancer resections	Operative and non-operative	AL rate 99/1048 (9.4%). Non-operative treatment 43/99(43.3%).
(Ogilvie, Dietz, and Stocchi 2012)	Patients following restorative proctosigmoidectomy for rectal cancer	Operative and non-operative	AL rate 130/991 (13.1%). Non-operative treatment of symptomatic patients occurred n=47/78 (60.3%). Total stoma reversal rate n=78/130 (60%)
(Ribeiro et al. 2019)	Patients following lower anterior resection	Operative and non-operative	AL rate 23/337 (6.8%). Non-operative treatment n=1/23 (4.3%), this was percutaneous drain. 30 day mortality n=5/23 (21.7%). Length of stay with AL 39.6 days, without AL 7.5 days. Antibiotic treatment 20/23 (87.0%)
(Rickles et al. 2013)	Patients following colectomies	Operative and non-operative	AL rate n=32/810 (4%). Length of stay with AL 20 days. Non-operative treatment n=8/32 (25%), of these n= 5/8 (62.5%) were percutaneous drain only and n=3/8 (37.5%) was antibiotic treatment.
(Schiff et al. 2017)	Patients following colorectal surgery and anastomosis formation and AL.		458 AL identified. Treatments, Over sewing of staple line n=355/458 (77.5%), use of sealant n=80/458 (17.5%), new anastomosis created n=43/458 (9.4%) and n=47/458 (10.3%) ileostomy/colostomy formation.
(Sirois-Giguère et al. 2013)	Patients after low anterior resection	Operative and non-operative	AL rate n=37/206 (18%). Non-operative treatment n=25/37 (67.6%). Non-operative success rate n=13/25 (52%), non-operative stoma reversal n=13/21 (61.9%). 30 day mortality rate n=1/37 (2.7%)
(Stafford et al. 2018)	Patients after left sided colorectal resections	Operative and non-operative	AL rate n= 2122/63748 (3.3%). Non-operative treatment n=1313/2122 (61.9%)
(Sultan, Chawla, and Zaidi 2014)	Patients with large intestinal anastomosis	Operative and non-operative	AL rate n=19/127 (15%). Non-operative treatment n=12/19 (63.2%), of non-operative treatments, n=10/12 (83.3%) were percutaneous drainage and n=2/12 (16.7%) were antibiotics. 30 day mortality rate n=3/19 (15.8%). Length of stay with AL 15 days, length of stay no AL 7.51 days.
(Tan et al. 2014)	Patients who underwent bowel resection and anastomosis		AL rate n=18/518 anastomoses (3.5%). Length of stay with AL 35.75 days, without AL 8.75 days

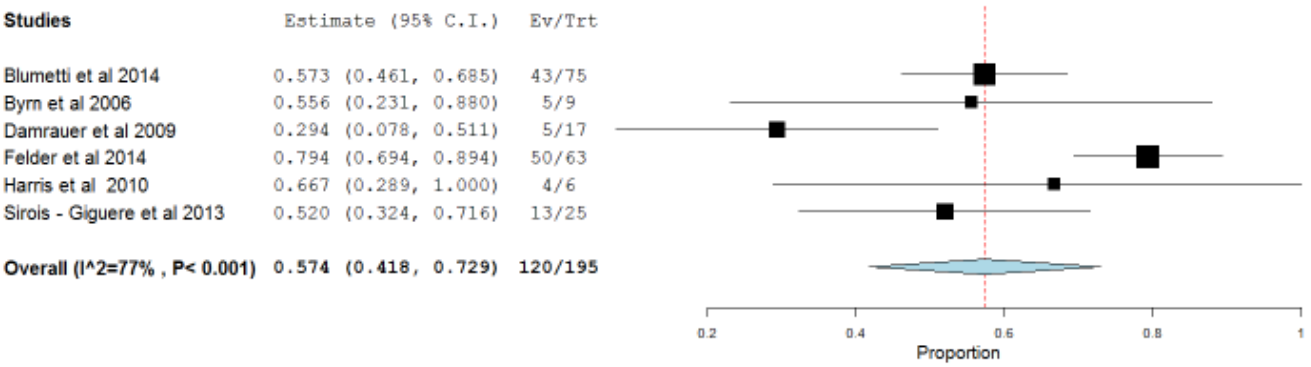
(Thornton et al. 2011)	Patients with anastomotic leak		Non-operative treatment, n=15/31 (48.4%). Stoma reversal rate n=23/30 (76.7%). 30 day mortality rate n=8/30 (26.7%).n=2 treated with percutaneous drain.

2 Meta-analysis used for Outcomes via Endo-SPONGE and Current AL Pathway

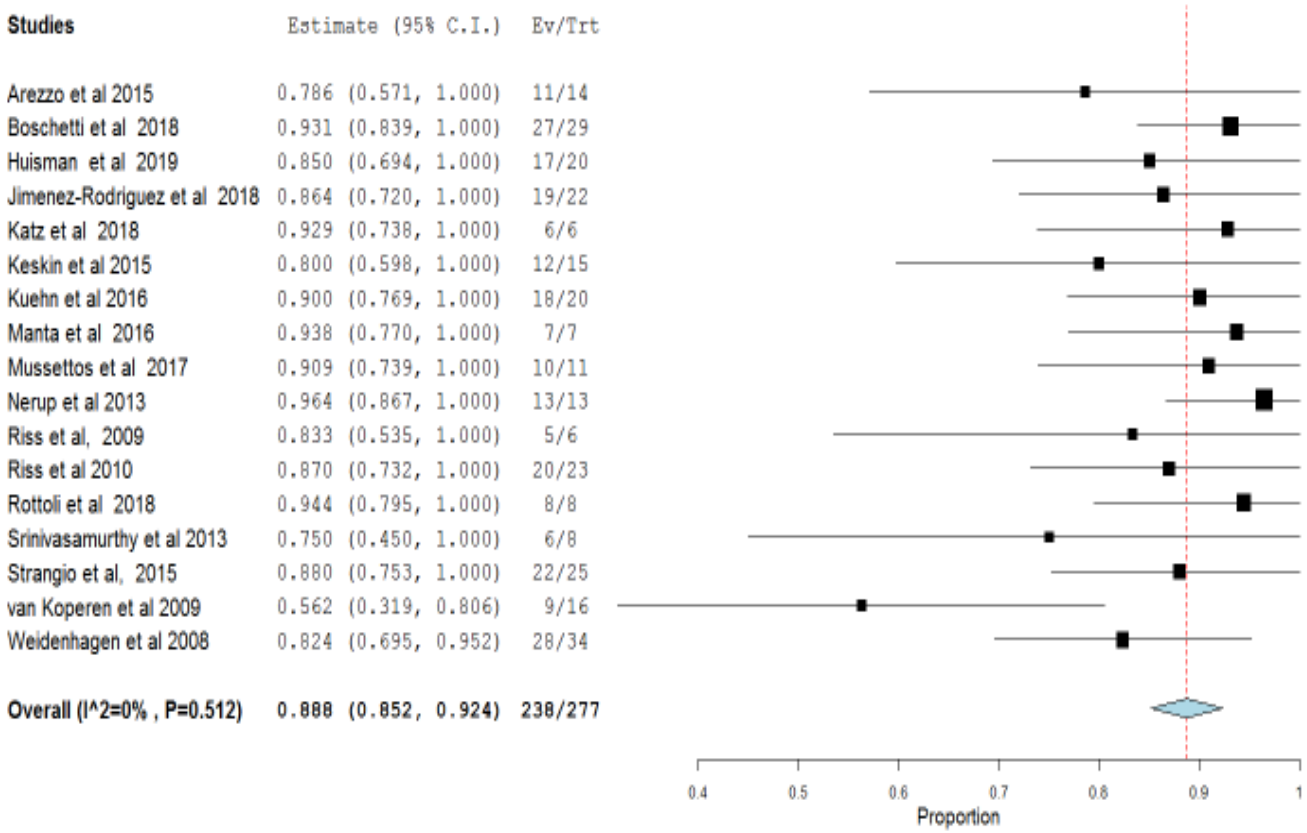
Currently out of 1933/4394 (44.0%) AL are treated by non-operative means. Binary regression demonstrated a weighted mean rate of non-operative treatment of AL of 42.8% (95% CI 30.4 to 55.2%) (I^2 = 99%).



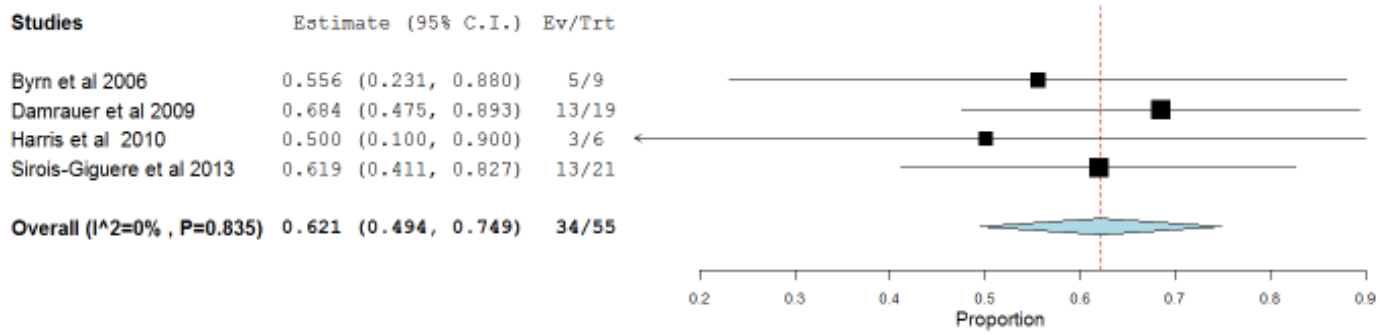
<u>Non operative current treatment success rate</u> was available from 6 studies covering 195 patients. From these studies 120/195 (60.82%). Binary regression demonstrated a weighted mean rate of non-operative successful healing of AL currently of 57.4% (95% CI 41.8 to 72.9%) (I^2 = 77%).



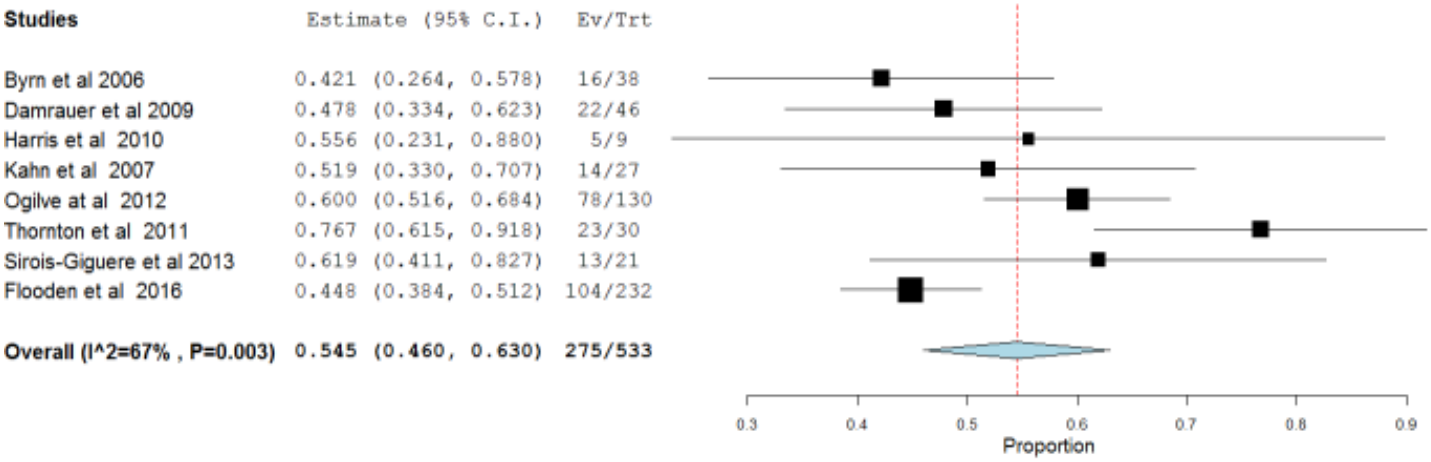
<u>Anastomosis healing rate Endo-SPONGE,</u> n=238/277 (85.9%). Random-effects meta-analysis showed that the weighted mean success rate of Endo-SPONGE was 88.8% (95% CI. 85.2 to 92.4) (I^2 =0%).



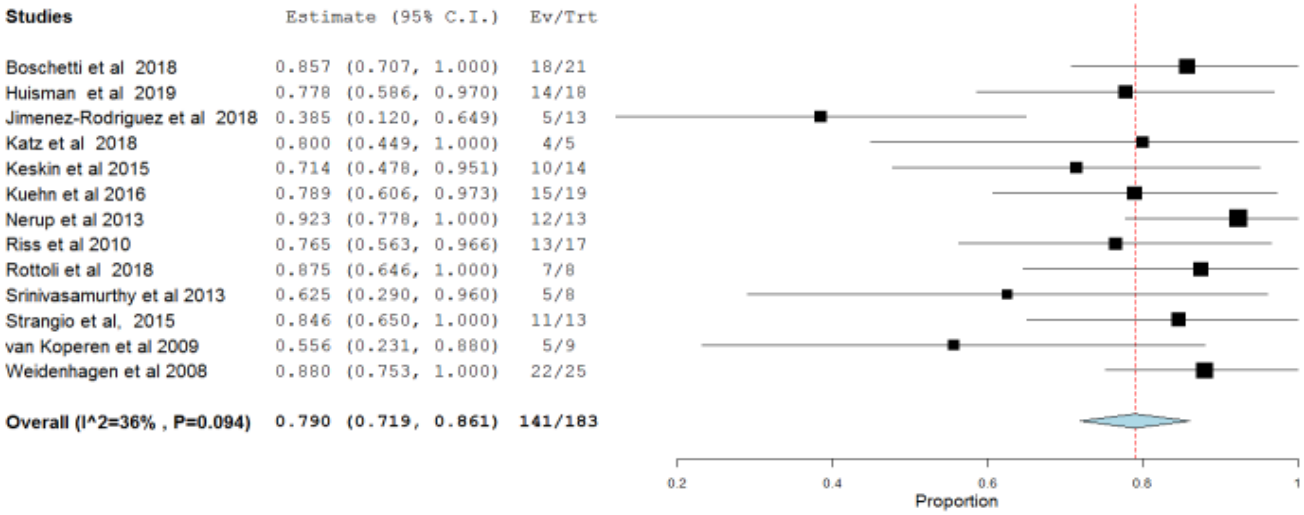
Stoma reversal rate following current non operative treatment was discussed in 4 studies with 34/551 (61.8%) patients successfully having their stoma reversed following non-operative treatment. Binary regression demonstrated a weighted mean rate of non-operative stoma reversal at 62.1% (95% CI 49.4 to 74.9%) (I^2 = 55%).



Stoma reversal – ALL current AL treatments (operative and non operative). Eight studies covered stoma reversal, with 275/533 (51.6%) patients successfully having their stoma reversed after an AL. Binary regression demonstrated a weighted mean rate for stoma reversal of 54.5% (95% CI 46.0 to 63.0%) (I^2 = 68%).

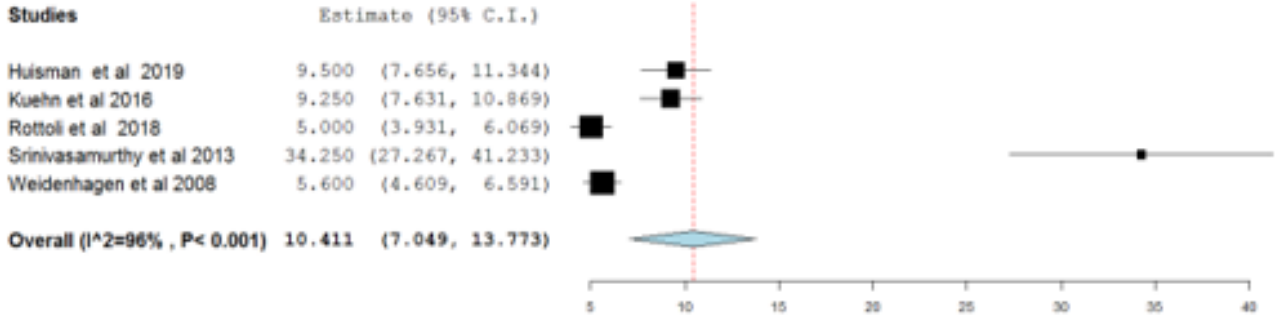


Stoma reversal rate Endo-SPONGE. A total of 183 patients had faecal diversion N=141/183 (77.0%) underwent reversal of stoma following successful treatment. Binary random-effects meta-analysis showed the weighted mean rate of stoma reversal across the studies to be 79.0% (95%CI 71.9 to 86.1) (I^2 = 36%).

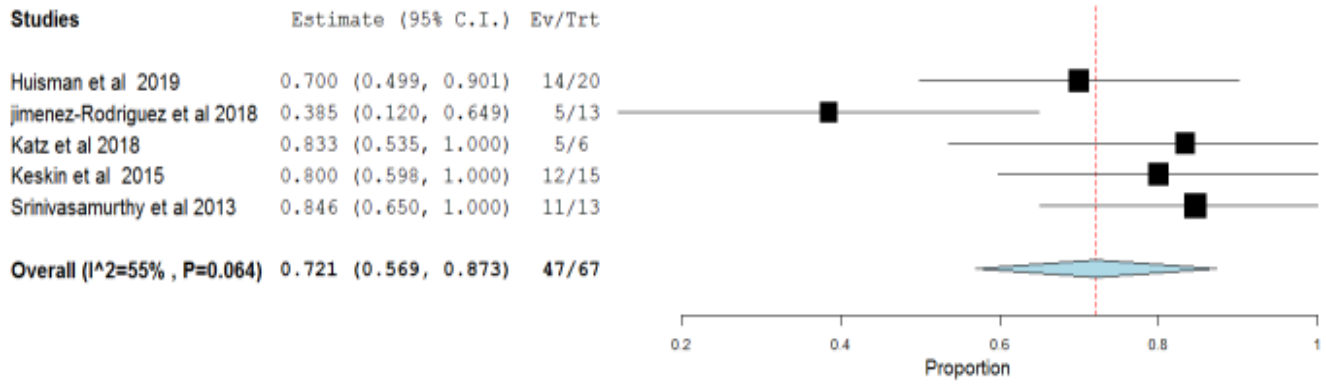


Time to stoma reversal was covered in only two studies for current AL treatment. Mean time to healing was reported as 10.6 (95% CI 7.55 to 13.62 months) by Harris et al and 10.23 months (95% CI 8.36 to 12.89 months) by Khan et al, (Harris et al. 2010; Khan et al. 2008).

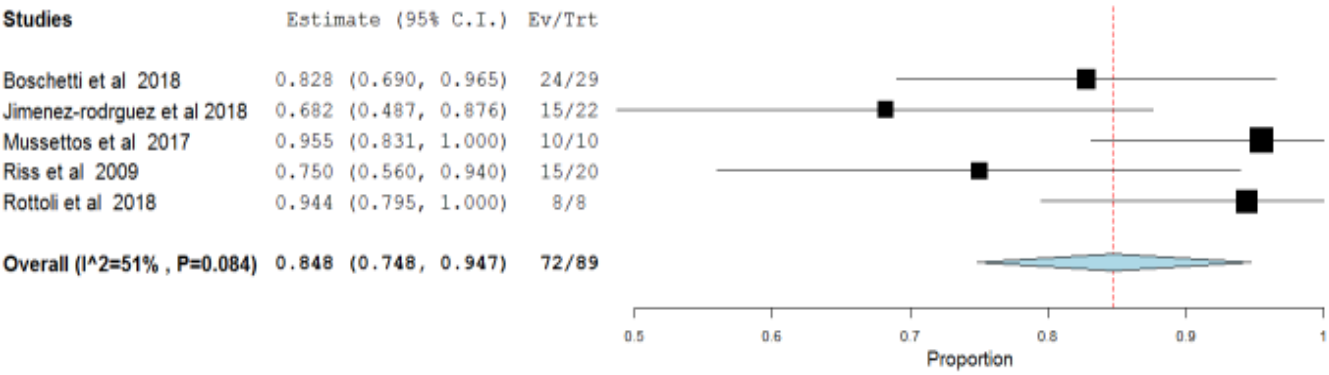
Time to stoma reversal Endo-SPONGE Binary random-effects meta-analysis showed the weighted mean time to stoma reversal was 10.41 months (95%CI 7.05 to 13.77 months) (I^2 =96%).



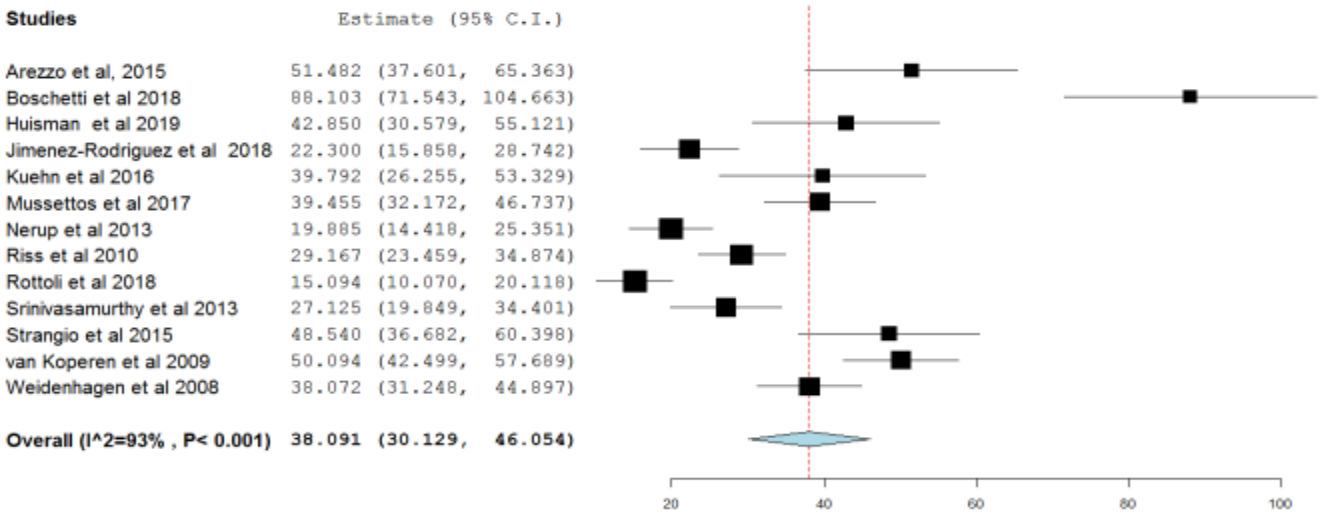
Bowel continuity Endo-SPONGE N=67 patients discussed bowel continuity, successful bowel continuity was achieved in 47/67 (70.1%) patients. Binary random-effects meta-analysis showed that the mean successful bowel continuity rate across the studies was 72.1% (95% CI 56.9 to 87.3) (I^2 =72.1).



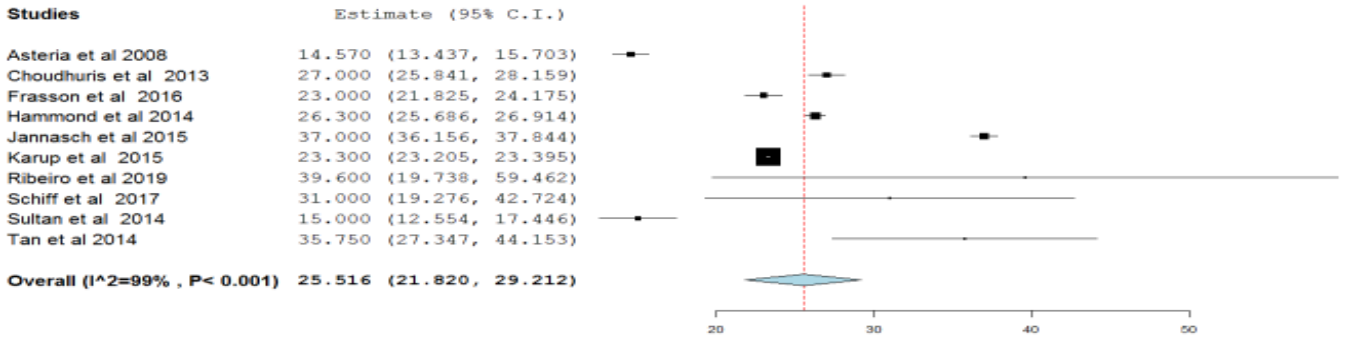
Long term success rate Endo-SPONGE Long term success was recorded for 89 patient. Of these 72/89 (80.9%) were reported as having long term successful healing of AL. Binary random -effects meta-analysis showed that the mean long term success rate across the studies was 84.8% (95% CI 74.8 to 94.7) (I^2 =51).



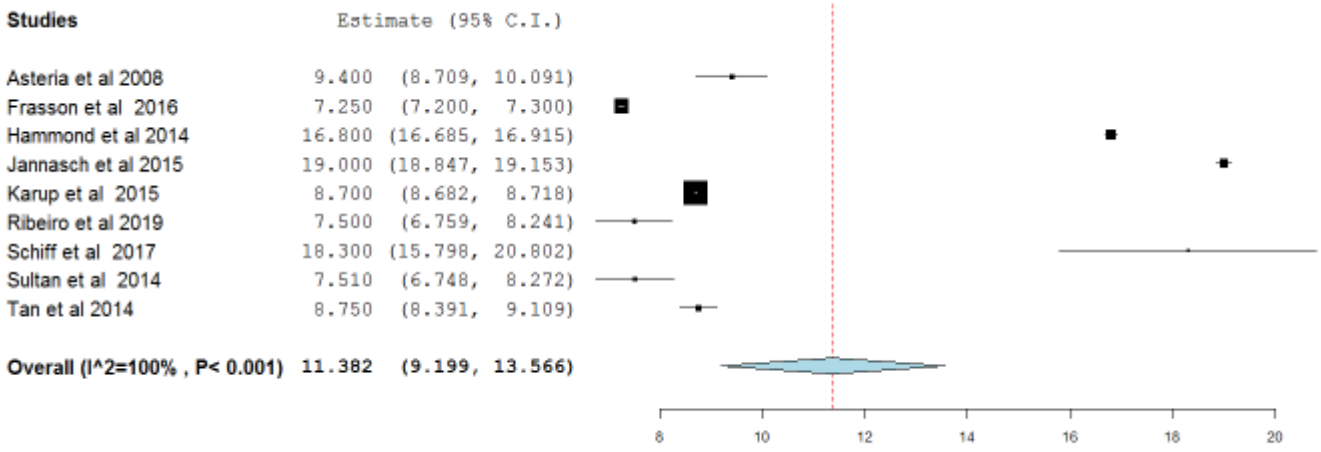
Treatment duration Endo-SPONGE Continuous random effects showed that the weighted mean duration of treatment was 38.1 days until closure of leak (95% CI 30.1 to 46.1 days) I^2 = 94%.



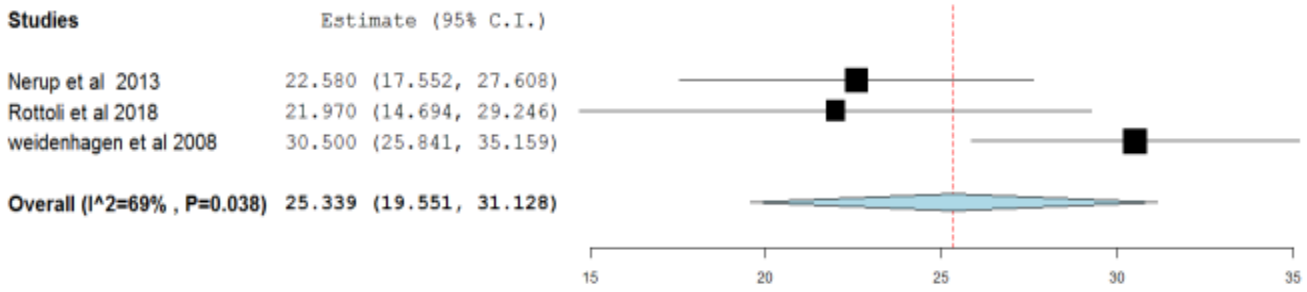
Length of stay (LOS) following current AL treatment was reported in 10 journal articles. Continuous regression demonstrated a weighted mean LOS with AL of 25.15 days (95% CI 21.82 to 29.21 days) (I^2 = 99%).



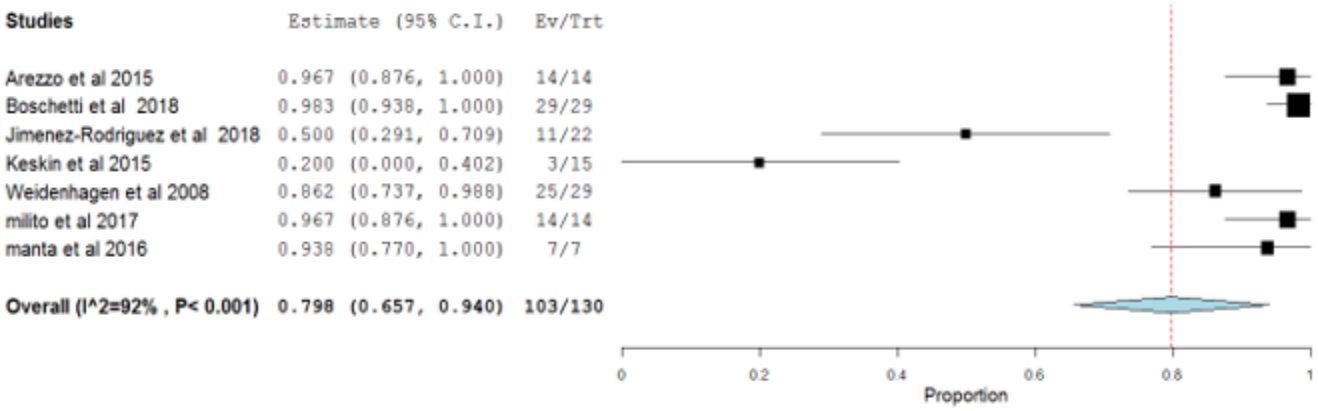
Length of stay WITHOUT AL was reported in 9 journal articles. Continuous regression demonstrated a weighted mean LOS without AL of 11.389 days (95% CI 9.199 to 13.566 days) (I^2 = 1000%).



In Patient LOS Endo-SPONGE was discussed in only 3 journal articles. Continuous random effects showed that the weighted mean LOS was 25.2 days (95% CI 19.6 to 31.1 days) (I^2 = 69%).

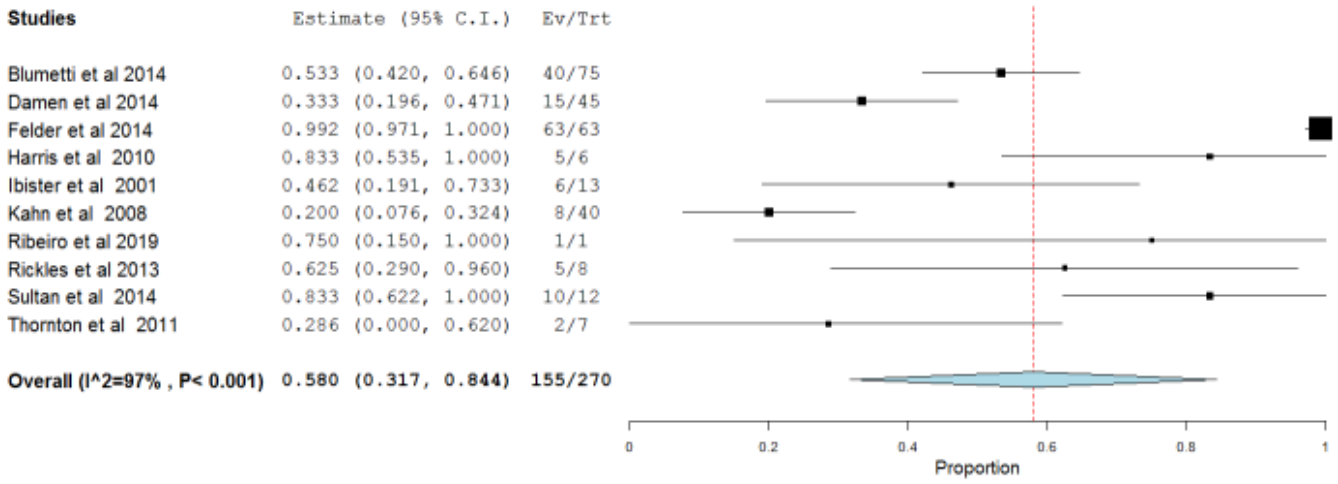


Outpatient use of Endo-SPONGE In or out patient use of Endo-SPONGE was discussed for 124 patients with 103/130 (79.2%). Binary random-effects meta-analysis showed that the weighted mean 79.8% of patient were treated as out patients (95% CI 65.7 to 94.0%) (I^2 =92%).

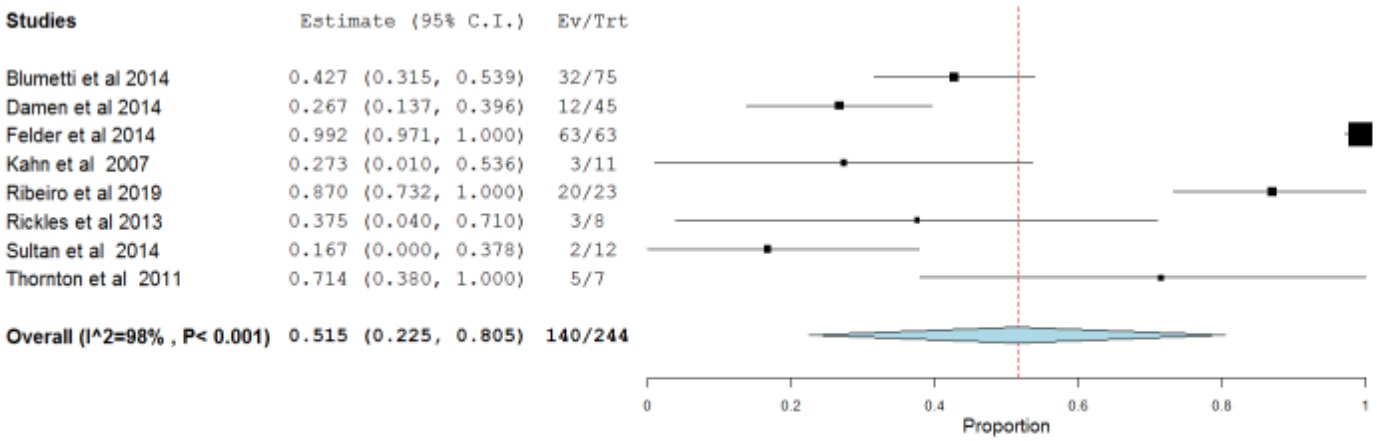


Current treatment – Percutaneous drainage.

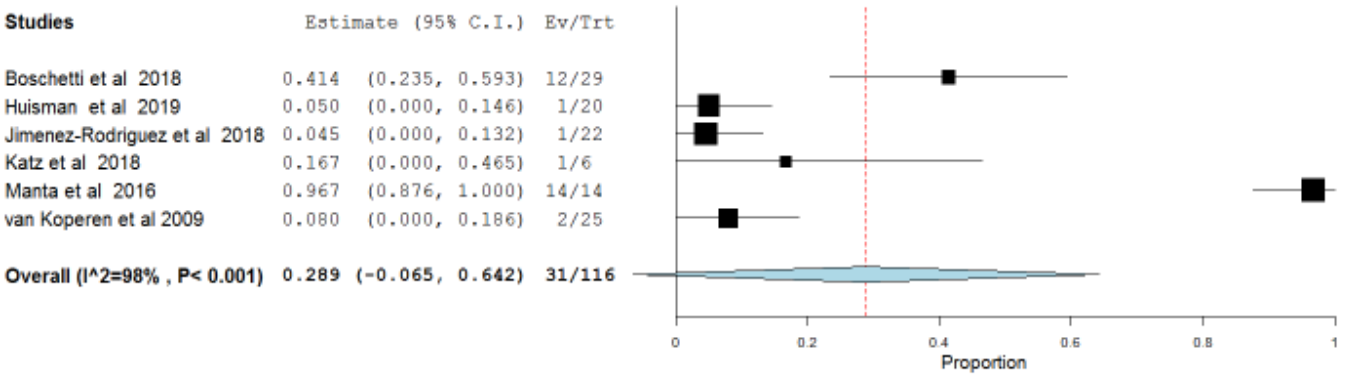
Of patients treated with a non-operative route 155/270 (64.4%) were treated with percutaneous drain. Binary regression demonstrated a weighted mean rate of percutaneous drain treatment (within non-operative group) of 58.0% (95% CI 31.7 to 84.4%) (I^2 = 97%).



Antibiotic use current treatment. Of patients treated with a non-operative route 140/244 (57.4%) were treated with antibiotics. Binary regression demonstrated a weighted mean rate of antibiotic treatment (within non-operative group) of 51.5% (95% CI 22.5 to 80.5%) (I^2 = 98%).



Antibiotic use with/before Endo-SPONGE. Overall 6 studies covering 116 patients discussed use of antibiotics before or during Endo-SPONGE use. Overall 31/116 (26.7%) patients were prescribed antibiotics alongside/ before use of Endo-SPONGE. Binary random-effects meta-analysis showed that the weighted mean 28.9% of patient were treated with antibiotics alongside/before Endo-SPONGE use (95% CI -6.45 to 64.2%) (I^2 =98%). In one study (Katz et al 2018) they had a standard treatment policy for use of antibiotics, rather than use of antibiotics depending on clinical needs n=14/14, this anomalous treatment process may have skewed the data



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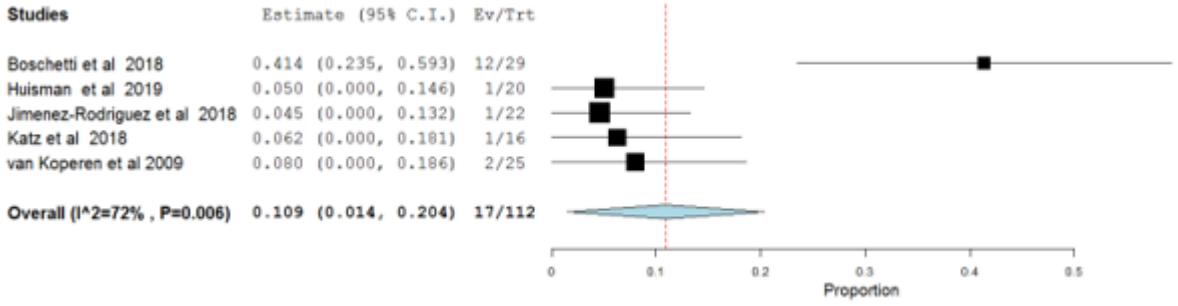
In 2 papers, n=13/49 (26.5%) patients were given antibiotic treatment before Endo-SPONGE treatment commenced.

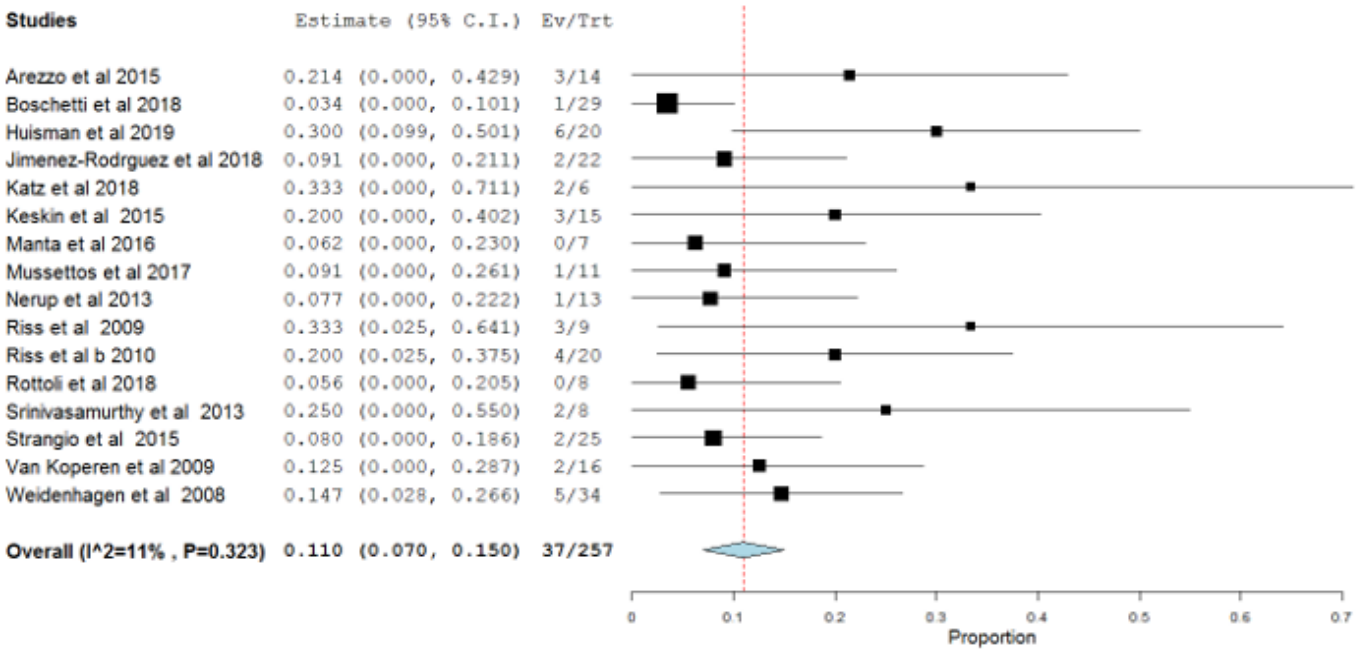
In 4 papers n= 18/67 (26.86%) patients were treated with antibiotic treatment during Endo-SPONGE treatment. In one study (Manta et al 2016) they had a standard treatment policy for use of antibiotics, rather

than use of antibiotics depending on clinical needs, this anomalous treatment process may have skewed the data.

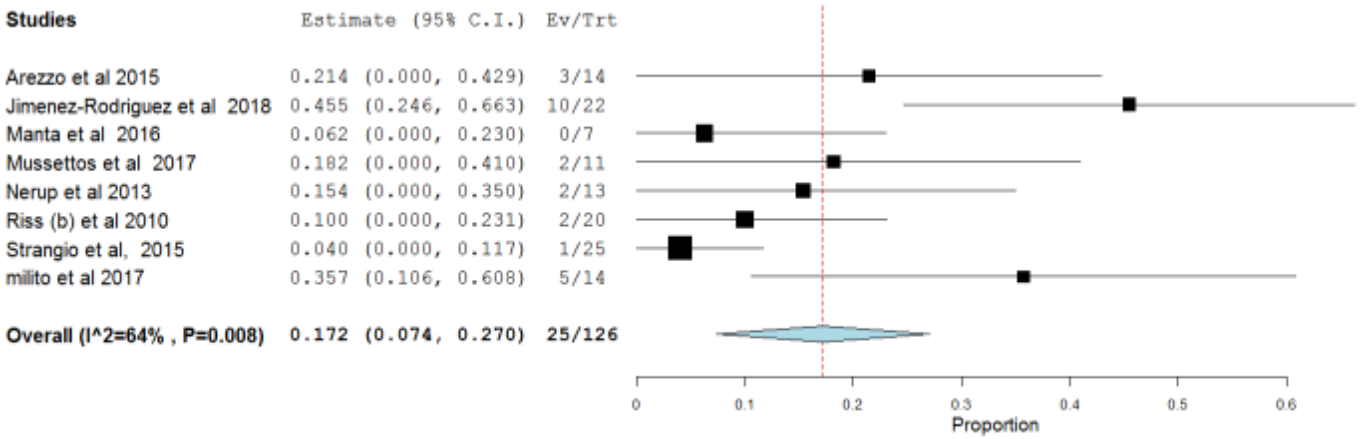
Antibiotic use with Endo-SPONGE – clinician choice. Clinicians chose to prescribe antibiotics alongside Endo-SPONGE in 5 studies covering 112 patients discussed use of antibiotics before or during Endo-SPONGE use. Overall 17/112 (15.2%) patients were prescribed antibiotics alongside/ before use of Endo-SPONGE. Binary random-effects meta-analysis showed that the weighted mean 10.9% of patient were treated with antibiotics alongside/before Endo-SPONGE use (95% CI 1.4 to 20.4%) (I^2 =72%).



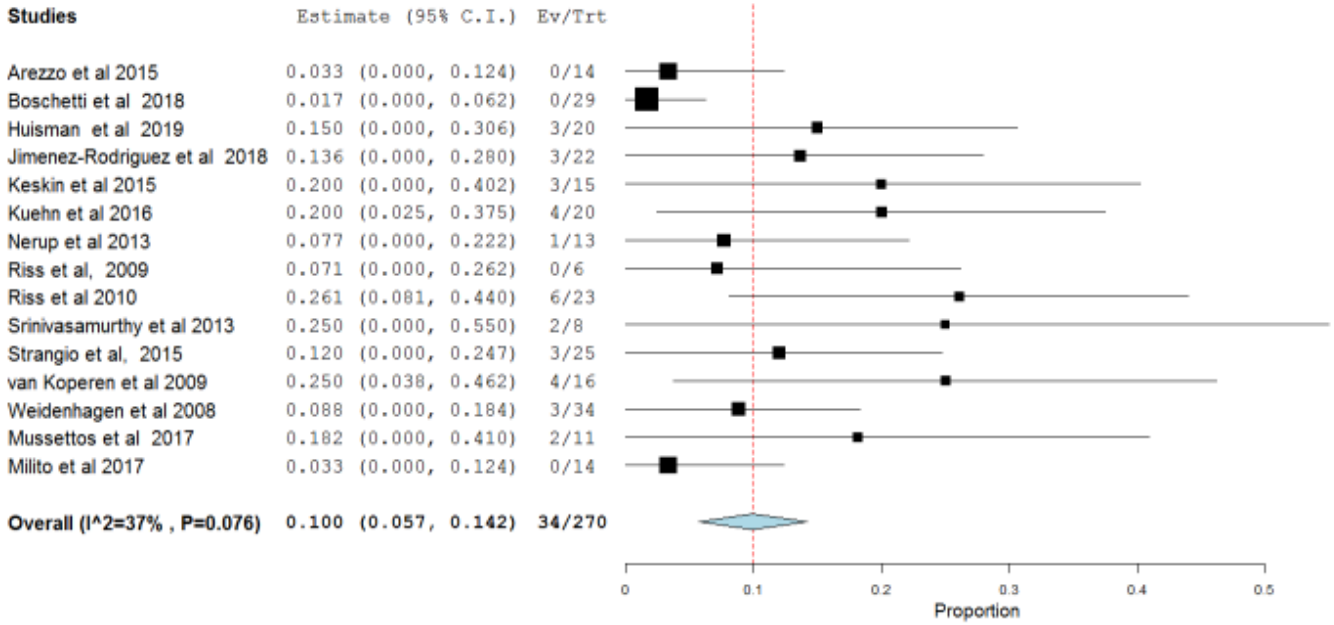
Extra Surgery Required Endo-SPONGE N=37/257 (14.3%) patients required addition surgery with Endo-SPONGE treatment. Binary random-effects meta-analysis showed that the mean additional surgery rate across the studies was 11.0% (95% CI 7.0 to 15.0) (I^2 =11).



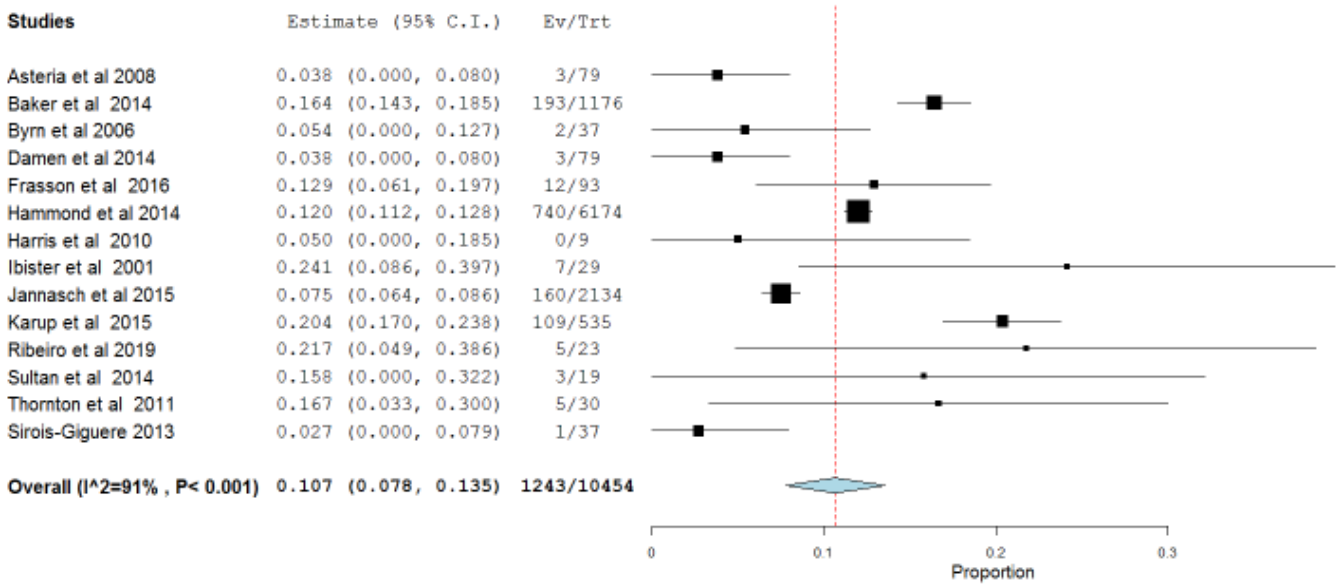
Additional endoscopic treatments **Endo-SPONGE** in 8 papers use of additional endoscopic treatment was reported in 25/126 (19.8%) in addition to Endo-SPONGE treatment. Binary random-effects meta-analysis showed that the weighted mean use of addition endoscopic treatment was 17.2% (95% CI 7.4 to 27.0) (I^2 =56). Other papers made no mention of complications. Details of extra endoscopic treatment are listed in data abstraction table in appendix A.



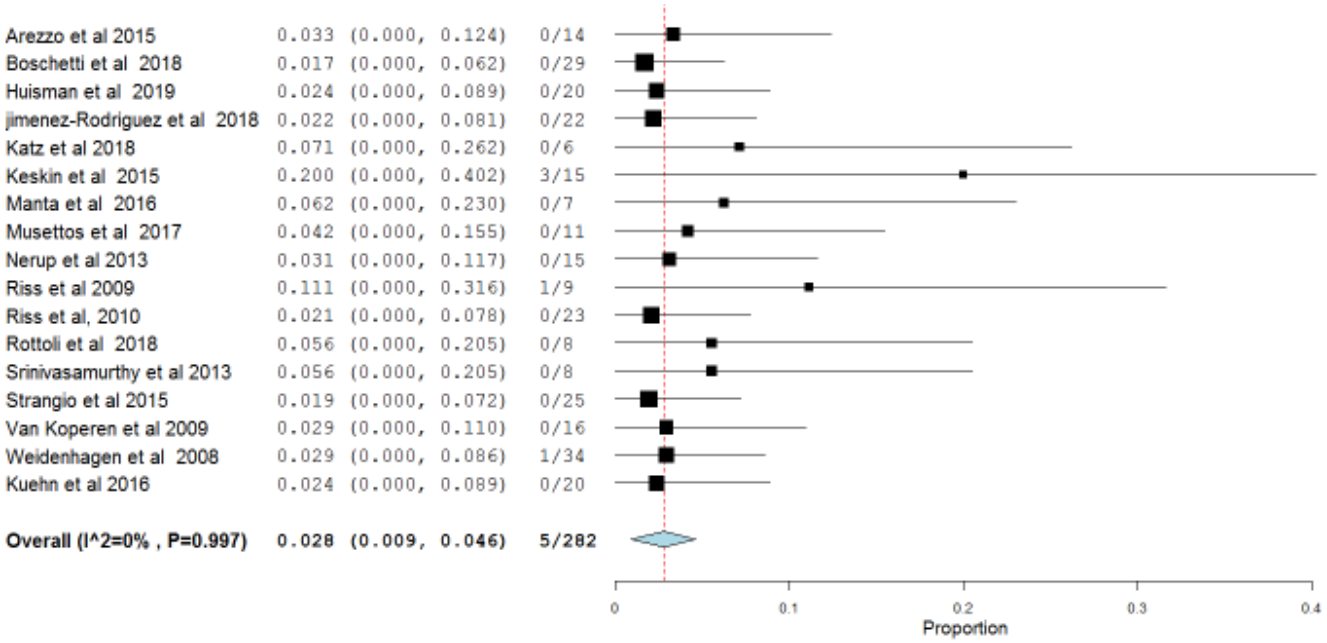
Complication rate **Endo-SPONGE** N=40/251 (15.9%) developed complications after Endo-SPONGE treatment. Binary random-effects meta-analysis showed that the mean complication rate across the studies was 13.6% (95% CI 7.8 to 19.4) (I^2 =56). Other papers made no mention of complications. Complications are listed in data abstraction table in appendix A.



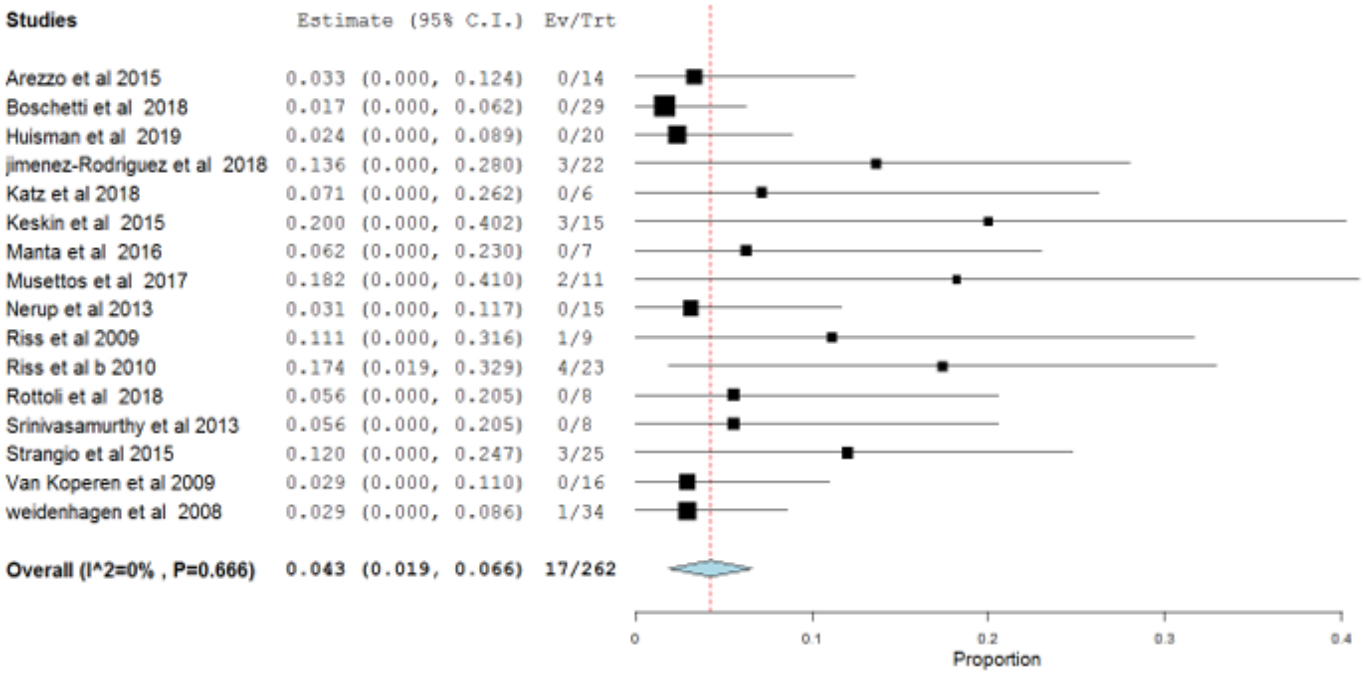
Current 30 day mortality following AL with all current treatment was covered in 14 papers with 1243/10,454 (11.8%) patients having 30 d mortality following AL. Binary regression demonstrated a weighted mean rate for 30 day mortality of 11.4% (95% CI 7.8 to 13.5%) (I^2 = 91%). Weighted mean could not be identified for non–operative treatment alone.



30 Day Mortality rate Endo-SPONGE overall n=5/282 (1.8%) patients had mortality within 30 days. Binary random-effects meta-analysis showed that the mean 30 day mortality rate across the studies was 2.8% (95% CI 0.9 to 4.6) (I^2 =0).



Overall Mortality overall Endo-SPONGE 17/262 (1.9%) patients died during long term follow up. Binary random-effects meta-analysis showed that the mean 30 day mortality rate across the studies was 4.3% (95% CI 1.9 to 6.66) (I^2 =0).



3 Details of relevant studies

Please give details of all relevant studies (all studies in table 1). Copy and paste a new table into the document for each study. Please use 1 table per study.

Arezzo et al 2015 Long term efficiency of endoscopic vacuum therapy for the treatment of colorectal anastomotic leaks	
What are main differences in resource use and clinical outcomes between the technologies?	Non comparative
How are the findings relevant to the decision problem?	Paper demonstrates that treatment of colorectal anastomotic leaks with Endo-SPONGE is successful (79%) and can be used in the outpatient setting, providing potential cost savings in n=14 patients.
Does this evidence support any of the claimed benefits for the technology? If so, which?	• Demonstrates Endo-SPONGE is a safe and highly efficient approach to treat colorectal anastomotic leaks (79% success rate and 0/14 complications, 0/14 30 day mortality). • Endo-SPONGE short treatment period compared healing was median 40.5 days (range 8–114). • Demonstrates use of Endo-SPONGE in outpatient setting rather than inpatient for n=14, chronic patient treated as outpatient initially white acute were treated as in patient for only 1 week, then moved to outpatient. – supports change from secondary to community care. • Reduced length of stay – patients treated as outpatients for all chronic leaks and as outpatient for acute after 1 week. • Less staff requirements – insertion of each sponge requires only 1 doctor and 1 nurse. • Demonstrates low level of surgical intervention required – 3/14 (21.5%). • Demonstrates successful treatment irrespective of neoadjuvant therapy (5/7, 71% success with NAR 6/7, 86% success without NAR) p=1.000. •
What cost analysis was done in the study? Please explain the results.	180 Euro per device 70 Euro for 15 minutes in Endoscopy suite – 1 Doctor and 1 nurse Median costs Euro 3,125 (range 1,000-10,000)
Will any information from this study be used in the economic model?	• Success rate 79%. • Median number of 12.5 sessions (range 4–40). • Further surgery was required in 3/14 (21.5%) cases.
What are the limitations of this evidence?	• It was uncontrolled and cannot rule out that some fistula would have closed without Endo-SPONGE treatment.

Arezzo et al 2015 Long term efficiency of endoscopic vacuum therapy for the treatment of colorectal anastomotic leaks	
	• Long recruitment period (4.5 years). It is possible that the surgical technique improved as the study progressed, which could have potentially affected the results • Being a retrospective analysis, subjects were not randomised to closure cohorts or followed prospectively. • Only patients who were treated by Endo-SPONGE have been included. • The number of patients was small and the group was somewhat heterogeneous.
How was the study funded?	No funding declared. No conflicts of interest to declare.

Boschetti et al (2018) Endo-SPONGE treatment of anastomotic leakage after colorectal surgery: A report of 29 cases compared to the main studies in the literature.	
What are main differences in resource use and clinical outcomes between the technologies?	Non comparative
How are the findings relevant to the decision problem?	Paper demonstrates that treatment of colorectal anastomotic leaks with Endo-SPONGE is successful (93%) and can be used in the outpatient setting without sedation in N=29 patients. Also provides information on long term continued success.
Does this evidence support any of the claimed benefits for the technology? If so, which?	• Demonstrates Endo-SPONGE is a safe and highly efficient approach to treat colorectal anastomotic leaks (93% success rate, 0/29 complications and 0/29 30 day mortality, high long term success rate 24/29). • Endo-SPONGE can prevent need for long term stoma – as 18/21 85.7% with a protective stoma successfully had stoma reversed, all reversed within 6 months. • Treatment with Endo-SPONGE can reduce need for antibiotics - twelve patients (41%) were on antibiotics before Endo-SPONGE treatment, after a few days (less than 10), the antibiotics were stopped. • Endo-SPONGE changes care from secondary to community care – Endo-SPONGE was inserted as an outpatient without sedation for all without sedation for all patients– reducing staff requirements. • Demonstrates Endo-SPONGE shortened treatment duration compared with conservative treatment - median treatment time 70 days (range 14-196). • Treatment was well tolerated. • Demonstrates low level of surgical intervention required – 1/29 (3.4%). • Reduction in number of patients with permanent stoma, direct impact on improved Quality of life by lack of stoma
What cost analysis was done in the study? Please explain the results.	• Treatment without sedation as outpatient.
Will any information from this study be used in the economic model?	• The cavity was closed in 27/29 (93%) patients. • 85.7% who presented with a stoma experienced a closure of the protective stoma. • Median number of applications 18.6 (range 4-57). • Further surgery required in 1/29 patients
What are the limitations of this evidence?	• It was uncontrolled and cannot rule out that some fistula would have closed without Endo-SPONGE treatment, however the authors report that over half of the patients were referred after failure of common management of AL. • It is a retrospective study without randomisation or controls • Only patients who were treated by Endo-SPONGE have been included.

Boschetti et al (2018) Endo-SPONGE treatment of anastomotic leakage after colorectal surgery: A report of 29 cases compared to the main studies in the literature.	
	• The number of patients was small and the group was somewhat heterogeneous.
How was the study funded?	No funding or conflicts of interest declared.

Clifford et al 2010 Early anastomotic complications in colorectal surgery: systematic review of techniques for endoscopic salvage	
What are main differences in resource use and clinical outcomes between the technologies?	Non comparative
How are the findings relevant to the decision problem?	Paper demonstrates that treatment of colorectal anastomotic leaks with Endo-SPONGE is successful (88%) in n=197 patients.
Does this evidence support any of the claimed benefits for the technology? If so, which?	• Demonstrates Endo-SPONGE is a safe and highly efficient approach to treat colorectal anastomotic leaks in 88.8% (range 66.6–100%) of patients.
What cost analysis was done in the study? Please explain the results.	None
Will any information from this study be used in the economic model?	No to prevent repetition of data from individual papers
What are the limitations of this evidence?	No meta-analysis involved, only descriptive systematic review.
How was the study funded?	No funding or conflicts of interest declared.

Huisman et al (2019) Effectiveness of Endo-SPONGE therapy for the management of presacral abscesses following rectal surgery	
What are main differences in resource use and clinical outcomes between the technologies?	Non comparative

Huisman et al (2019) Effectiveness of Endo-SPONGE therapy for the management of presacral abscesses following rectal surgery	
How are the findings relevant to the decision problem?	Paper demonstrates that treatment of colorectal anastomotic leaks with Endo-SPONGE is successful (85%) in n=20 patients.
Does this evidence support any of the claimed benefits for the technology? If so, which?	• Demonstrates Endo-SPONGE is a safe and highly efficient approach to treat colorectal anastomotic leakage. (N = 17/20 (85%) of patients successful AL healing, N=3/20 complications, 0/20 30 day mortality) • Endo-SPONGE can prevent need for long term stoma/ restore bowel continuity in 14/20 patients (70%), reversal within 7 months in the early treatment group and 10 months in the late treatment group. • Low requirement of extra surgery N=6/20 (30%) • Low level of antibiotic use with Endo-SPONGE (N=1/20 patient was on antibiotics) • Short treatment (Median 9 (2-28) sponge changes, Median treatment duration 25 days (3-115)) • Reduction in number of patients with permanent stoma, direct impact on improved Quality of life by lack of stoma
What cost analysis was done in the study? Please explain the results.	• None
Will any information from this study be used in the economic model?	• Endo-SPONGE successful (closed leak) in 17/20 (85%) of patients. • 14/20 patients (70%) continuity was restored/stoma reversal. • Further surgery required in 6/20 patients • Median 9 (2-28) sponge changes.
What are the limitations of this evidence?	• It was uncontrolled and cannot rule out that some fistula would have closed without Endo-SPONGE treatment. • It is a retrospective study in which only patients who were treated by Endo-SPONGE have been included. • The number of patients was small and the group was somewhat heterogeneous. • LARS data is compared with patients who did not have an AL – difficult to ascertain if LARS score is due to treatment of AL or AL itself.
How was the study funded?	No funding or conflicts of interest declared.

Jimenez-Rodriguez et al A New Perspective on Vacuum-Assisted Closure for the Treatment of Anastomotic Leak Following Low Anterior Resection for Rectal Cancer, Is It Worthy?	
What are main differences in resource use and clinical outcomes between the technologies?	Non comparative

Jimenez-Rodriguez et al A New Perspective on Vacuum-Assisted Closure for the Treatment of Anastomotic Leak Following Low Anterior Resection for Rectal Cancer, Is It Worthy?	
How are the findings relevant to the decision problem?	Paper demonstrates that treatment of colorectal anastomotic leaks with Endo-SPONGE is successful (86%) in n=22 patients, with rapid healing in mean 22.3 days.
Does this evidence support any of the claimed benefits for the technology? If so, which?	• Demonstrates Endo-SPONGE is a safe and highly efficient approach to treat colorectal anastomotic leaks (Success rate N=19/22, 86%, Low complication 0/22 during treatment, n=3/22 long term complications, low mortality, 0/22 30 day mortality, n=3/22 long term mortality.). • Demonstrates Endo-SPONGE short treatment duration with rapid healing mean 22.3 days ± 14.7. • Endo-SPONGE changes care from secondary to community care – half of patients were treated as outpatients after initial application. • Reduced length of stay - half of patients were treated as outpatients after initial application. • Endo-SPONGE is well tolerated - all patients experienced discomfort that was well tolerated and that decreased as the size of the sponge introduced decreased. • Endo-SPONGE reduce permanent stoma, N=5/13 stoma reversed • Low complication rate - no patient experienced complications while the treatment was being performed. • Low need for additional surgery – N=2/22 (9%) extra surgery required • Reduction in number of patients with permanent stoma, direct impact on improved Quality of life by lack of stoma
Will any information from this study be used in the economic model?	• Successful colorectal anastomotic leak closure (n=19/22, 86%). • Half of patients were treated as outpatients after initial application. • Extra surgery requirements N=2/22 • Stoma reversal 5/13 • Median 3.1±1.9 sponge changes
What cost analysis was done in the study? Please explain the results	• Cost of ambulatory stay US$ 80
What are the limitations of this evidence?	• It was uncontrolled and cannot rule out that some fistula would have closed without Endo-SPONGE treatment. • It is a retrospective study in which only patients who were treated by Endo-SPONGE have been included. • The number of patients was small and the group was somewhat heterogeneous.
How was the study funded?	The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: CIBEREHD was funded by the Instituto de Salud Carlos III, Madrid, Spain. No conflicts of interest declared.

Katz et al 2018 Different approaches for Endo-SPONGE® insertion to treat rectal anastomotic leaks	
What are main differences in resource use and clinical outcomes between the technologies?	Non comparative
How are the findings relevant to the decision problem?	Paper demonstrates that treatment of colorectal anastomotic leakage with Endo-SPONGE is successful (100%) in n=6 patients.
Does this evidence support any of the claimed benefits for the technology? If so, which?	• Demonstrates Endo-SPONGE is a safe and highly efficient approach to treat colorectal anastomotic – all (100%) patients fully recovered=0/6 30 day mortality. • Endo-SPONGE can prevent need for long term stoma/ restore bowel continuity, 4/5 (80%) stoma was reversed and 5/6 (83%) regained bowel continuity. • Reduce costs by outpatient treatment – n=3/15 patients treated as out patient • Endo-SPONGE controls sepsis, n=6/6 patients sepsis was controlled. • Reduction in number of patients with permanent stoma, direct impact on improved Quality of life by lack of stoma
What cost analysis was done in the study? Please explain the results.	None
Will any information from this study be used in the economic model?	Mean Endo-SPONGE application was 3.6 (range 3-5). Stoma reversed in n=4/5 patients Successful AL healing in n=6/6
What are the limitations of this evidence?	• It was uncontrolled and cannot rule out that some fistula would have closed without Endo-SPONGE treatment. • It is a retrospective study in which only patients who were treated by Endo-SPONGE have been included. • The number of patients was small and the group was somewhat heterogeneous. • Limited details reported.
How was the study funded?	No funding or conflicts of interest declared.

Keskin et al 2015 Effectiveness of Endoluminal Vacuum-assisted Closure Therapy (Endo-SPONGE) for the Treatment of Pelvic Anastomotic Leakage After Colorectal Surgery	
What are main differences in resource use and clinical outcomes between the technologies?	Non comparative
How are the findings relevant to the decision problem?	Paper demonstrates that treatment of colorectal anastomotic leakage with Endo-SPONGE is successful (80%) in n=15 patients.
Does this evidence support any of the claimed benefits for the technology? If so, which?	• Demonstrates Endo-SPONGE is a safe and highly efficient approach to treat colorectal anastomotic leakage, n=12/15 (80%) successful AL healing, n=0/15 30 day mortality and 3/15 long term mortality, n=3/15 complications) • Endo-SPONGE can prevent need for long term stoma/ restore bowel continuity, n=10/14 (71%) stoma reversed and n=12/15 (67%) lumen integrity achieved. • Reduction in number of patients with permanent stoma, direct impact on improved Quality of life by lack of stoma • Endo-SPONGE reduced costs by reduced need for surgery n=3/15 required extra surgery.
What cost analysis was done in the study? Please explain the results.	• None
Will any information from this study be used in the economic model?	• Average 2.2 Endo-SPONGE applications (range 1-5). • Low need for extra surgery n=3/15 • Stoma reversal; 10/14 • Median 2.2 (1-5) sponge exchanges needed
What are the limitations of this evidence?	• It was uncontrolled and cannot rule out that some fistula would have closed without Endo-SPONGE treatment. • It is a retrospective study in which only patients who were treated by Endo-SPONGE have been included. • The number of patients was small and the group was somewhat heterogeneous.
How was the study funded?	No funding or conflicts of interest declared.

Kuehn et al 2016 Endoscopic Vacuum Therapy in Colorectal Surgery	
What are main differences in resource use and clinical outcomes between the technologies?	Non comparative
How are the findings relevant to the decision problem?	Paper demonstrates that treatment of colorectal anastomotic leakage with Endo-SPONGE is successful (90%) in n=20 patients.
Does this evidence support any of the claimed benefits for the technology? If so, which?	• Demonstrates Endo-SPONGE is a safe and highly efficient approach to treat colorectal anastomotic leakage (n=18/20, 90% successful AL healing, 0/20 30 day mortality rate, 4/20 complications). • Endo-SPONGE can prevent need for long term stoma/ restore bowel continuity, closure of protective enterostomy was possible in 15 of 19 patients (79 %) within 244 days. • Endo-SPONGE supports control of sepsis with sepsis controlled in 27/32 patients. • Reduction in number of patients with permanent stoma, direct impact on improved Quality of life by lack of stoma • Demonstrates Endo-SPONGE short treatment duration, median duration of therapy 23 days (range 2-109). • Reduce length of time with stoma, median time to closure of enterostomy was 244 days (range, 152–488).
What cost analysis was done in the study? Please explain the results.	• None
Will any information from this study be used in the economic model?	• AL sucessful healing n=18/20 • Stoma reversal n=15/19 • Medain 6 (1-37) sponge exchanges
What are the limitations of this evidence?	• It was uncontrolled and cannot rule out that some fistula would have closed without Endo-SPONGE treatment. • It is a retrospective study in which no randomisation was used • Single centre study • Only patients who were treated by Endo-SPONGE have been included. • Outcome presented by participant group rather than individually
How was the study funded?	No funding or conflicts of interest declared.

Manta et al 2016 Endoscopic management of patients with post-surgical leaks involving the gastrointestinal tract: a large case series	
What are main differences in resource use and clinical	Non comparative

Manta et al 2016 Endoscopic management of patients with post-surgical leaks involving the gastrointestinal tract: a large case series	
outcomes between the technologies	
How are the findings relevant to the decision problem?	Paper demonstrates that treatment of colorectal anastomotic leaks with Endo-SPONGE is successful (100%) in n=7 patients without further interventions.
Does this evidence support any of the claimed benefits for the technology? If so, which?	• Demonstrates Endo-SPONGE is a safe and highly efficient approach to treat colorectal anastomotic leaks (100% successful AL healing n=7/7 patients, 0/7 30 day mortality rate) • Demonstrates low level of surgical intervention required – none of the 7 Endo-SPONGE patients required any other intervention, other endoscopic treatments required addition interventions for some patients. • Endo-SPONGE changes care from secondary to community care, initial treatment performed as inpatient then as an outpatient, for n=7/7. • Demonstrates reduced impact of hospital resource as all patients were treated as out patients
What cost analysis was done in the study? Please explain the results.	None
Will any information from this study be used in the economic model?	N=7/7 (100%) successful leak closure. N=0/7 extra surgery required
What are the limitations of this evidence?	Retrospective study with focus on all endoscopic events and limited detail provided on each individual endoscopic treatment. Small number of exposure to Endo-SPONGE in study.
How was the study funded?	This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Milito, et al 2017. Endoluminal Vacuum Therapy as Treatment for Anastomotic Colorectal Leakage.	
What are main differences in resource use and clinical outcomes between the technologies?	Non comparative
How are the findings relevant to the decision problem?	Paper discusses use of Endo-SPONGE reporting on complications
Does this evidence support any of the claimed benefits for the technology? If so, which?	Endo-SPONGE is well tolerated, 5/14 patients reporting mild but manageable pain, with no need to suture the defect
What cost analysis was done in the study? Please explain the results	None
Will any information from this study be used in the economic model?	No
What are the limitations of this evidence?	Details of actual outcome not clear – implies all leaks healed, however this is not actually addressed in the results. Small sample size Only treatment with Endo-SPONGE was included
How was the study funded?	No funding declared. No conflicts of interest.

Mussetto et al 2017 Long term efficacy of vacuum-assisted therapy (Endo-SPONGE) in large anastomotic leakages following anterior rectal resection	
What are main differences in resource use and clinical outcomes between the technologies	Non comparative
How are the findings relevant to the decision problem?	Paper demonstrates long term success in N=10/10 (100%) patients treated with Endo-SPONGE
Does this evidence support any of the claimed benefits for the technology? If so, which?	• Demonstrates Endo-SPONGE is a safe and highly efficient approach to treat colorectal anastomotic leaks (91% initial successful AL healing n=10/11 patients, 100% long term success N=10/10, 0/7 30 day mortality rate, 2/11 long term mortality rate 2/11 complication rate) • Demonstrates low need for extra surgery with n=1/22 (9%) following Endo-SPONGE treatment
What cost analysis was done in the study? Please explain the results.	• None
Will any information from this study be used in the economic model?	• Initial success rate n=10/11 (91%) • Median 16 (9-23) sponge changes.
What are the limitations of this evidence?	• It was uncontrolled and cannot rule out that some fistula would have closed without Endo-SPONGE treatment. • It is a retrospective study in which no randomisation was used • Single centre study • Only patients who were treated by Endo-SPONGE have been included. • Outcome presented by participant group rather than individually
How was the study funded?	No funding or conflicts of interest declared.

Nerup et al 2013 Promising results after endoscopic vacuum treatment of anastomotic leakage following resection of rectal cancer with ileostomy	
What are main differences in resource use and clinical outcomes between the technologies?	Non comparative
How are the findings relevant to the decision problem?	Paper demonstrates that treatment of colorectal anastomotic leakage with Endo-SPONGE is successful (100%) in n=13 patients.
Does this evidence support any of the claimed benefits for the technology? If so, which?	• Demonstrates Endo-SPONGE is a safe and highly efficient approach to treat colorectal anastomotic leakage (N=13/13 successful healing of anastomotic cavity, N=1/13 complications, n=0/13 30 day mortality) • Endo-SPONGE can prevent need for long term stoma/ restore bowel continuity, N=12/13 (92%) stoma closure rate of the entire study group. • Endo-SPONGE changes care from secondary to community care – some continued treatment in an outpatient setting. • Endo-SPONGE has low need for extra surgery, N=1/13. • Endo-SPONGE provides short treatment duration 37 days (18-65)
What cost analysis was done in the study? Please explain the results.	• None
Will any information from this study be used in the economic model?	• N=13/13 successful healing of anastomotic cavity. • N=12/13 (92%) stoma closure rate of the entire study group. • Median length of stay in hospital 25 days (7-39). • Median number of treatments 8 (1-18). • Need for extra surgery N=1/13
What are the limitations of this evidence?	• It was uncontrolled and cannot rule out that some fistula would have closed without Endo-SPONGE treatment. • It is a retrospective study in which only patients who were treated by Endo-SPONGE have been included. • Small sample size.
How was the study funded?	No funding or conflicts of interest declared

Popivanov et al 2019 Endoluminal negative pressure therapy in colorectal anastomotic leaks	
What are main differences in resource use and clinical outcomes between the technologies?	Non comparative
How are the findings relevant to the decision problem?	A systematic review of relevant papers using Endo-SPONGE for treatment of colorectal anastomotic leak demonstrating overall success of 85.4% of leak closure and 72.6% stoma closure rate in 295 patients.
Does this evidence support any of the claimed benefits for the technology? If so, which?	• Demonstrates Endo-SPONGE is a safe and highly efficient approach to treat colorectal anastomotic leak, success rate was 85.4% (80%–91%). • Endo-SPONGE can prevent need for long term stoma/ restore bowel Ileostomy closure was achieved in 72.6%. • Low complication rate. Complications were observed in 19% (13%–25%). •
What cost analysis was done in the study? Please explain the results.	• None
Will any information from this study be used in the economic model?	• No to prevent using data from original sources more than once
What are the limitations of this evidence?	The limitations are related to the small sample size, the retrospective nature of most of the studies and the lack of large comparative series.
How was the study funded?	No funding or conflicts of interest declared.

Riss et al 2009 Endo-SPONGE assisted treatment of anastomotic leakage following colorectal surgery	
What cost analysis was done in the study? Please explain the results.	Non comparative
How are the findings relevant to the decision problem?	Paper demonstrates that initial treatment of colorectal anastomotic leakage and rectal stump insufficiently with Endo-SPONGE is successful (83%) in n=6 patients.
Does this evidence support any of the claimed benefits for the technology? If so, which?	• Demonstrates Endo-SPONGE is a safe and highly efficient approach to treat colorectal anastomotic leakage (N=5/6 (83.3%) healed for anastomotic leak after rectal resection (n=1/6 required surgery), Complication rate n=6/23 (30%), 30 day mortality n=1/9 (heart attack). • Treatment was well tolerated, patients satisfaction VAS 0 = best, 10 = worst, median = 3 (range 0-9). Alteration in daily life, median = 5 (range 1-9). Pain, median = 3 (range 0-6) • Low complication rate, no complication's observed while using Endo-SPONGE. • Low need for extra surgery n=3/9 (33%) •
What cost analysis was done in the study? Please explain the results	• Duration of Endo-Sponge insertion 15 minutes, range 5-65
Will any information from this study be used in the economic model?	• N=5/6 (83.3%) healed for anastomotic leak after rectal resection. • N=3/6 required surgery. • The median duration of each Endo-SPONGE replacement was 15 min (range: 5– 65).
What are the limitations of this evidence?	• It was uncontrolled and cannot rule out that some fistula would have closed without Endo-SPONGE treatment. • It is a retrospective study in which only patients who were treated by Endo-SPONGE have been included. • Small sample size. • Study was not solely focussed on anastomotic leaks.
How was the study funded?	No funding or conflicts of interest declared.

Riss et al 2010 Recurrent abscess after primary successful Endo-SPONGE treatment of anastomotic leakage following rectal surgery	
What are main differences in resource use and clinical outcomes between the technologies?	Non comparative
How are the findings relevant to the decision problem?	Paper demonstrates that initial treatment of colorectal anastomotic leakage with Endo-SPONGE is successful (87%) in n=23 patients. Long term follow up of n=20 successful treatments demonstrated 75% long term success.
Does this evidence support any of the claimed benefits for the technology? If so, which?	• Demonstrates Endo-SPONGE is a safe and highly efficient approach to treat colorectal anastomotic leakage, (n=20/23 Endo-SPONGE treatments initially successful (87%) and n=5/20 (25%) developed recurrent symptomatic abscess, long term mortality n=4/23, 30 day mortality rate n=0/23) • Demonstrates Endo-SPONGE reduces permanent stoma, Reversal rate N=13/17 (76.5%) • Short treatment duration median 21 days (14-56) • Demonstrates Endo-SPONGE has low need for further surgery N=3/20 additional surgery
What cost analysis was done in the study? Please explain the results.	• None
Will any information from this study be used in the economic model?	• N=20/23 Endo-SPONGE treatments initially successful (87%). • Stoma reversal N=13/17 (76.5%) • Extra surgery required N=13/20
What are the limitations of this evidence?	• It was uncontrolled and cannot rule out that some fistula would have closed without Endo-SPONGE treatment. • It is a retrospective study in which only patients who were treated by Endo-SPONGE have been included. • Small sample size.
How was the study funded?	No funding or conflicts of interest declared.

Rottoli et al 2018 Endoluminal vacuum-assisted therapy as treatment for anastomotic leak after ileal pouch-anal anastomosis: a pilot study	
What are main differences in resource use and clinical outcomes between the technologies?	Non comparative
How are the findings relevant to the decision problem?	Paper demonstrates that initial treatment of colorectal anastomotic leakage with Endo-SPONGE is successful (100%) in n=8 patients.
Does this evidence support any of the claimed benefits for the technology? If so, which?	• Demonstrates Endo-SPONGE is a safe and highly efficient approach to treat colorectal anastomotic leakage (100%), at a median follow-up time of 11.6 (6–18) months after confirmation of the healing of the anastomotic leak, no recurrence was documented. • Demonstrates Endo-SPONGE short treatment duration, treatment lasted for a median of 12 (3–32) days. • Reduced length of stay, the median length of hospital stay after the first application of the treatment was 15.5 (6–48) days. Overall, the median length of hospital stay (including the postoperative stay from the pouch surgery in seven cases and the closure of ileostomy in one case) was 32 (16–72) days. • Endo-SPONGE can prevent need for long term stoma/ restore bowel continuity. All patients but one (n=7/8, 87.5%) had their ileostomy reversed at a median of 2.5 (1–6) months from the endoscopic confirmation of healing. • Treatment was well tolerated, No patients reported incontinence of faeces or gas. • Demonstrates low need for additional surgery n=1/8 required surgery following Endo-SPONGE treatment
What cost analysis was done in the study? Please explain the results.	None
Will any information from this study be used in the economic model?	• The median length of hospital stay after the first application of the treatment was 15.5 (6–48) days. • N=7/8 (87.5%) had their ileostomy reversed at a median of 2.5 (1–6) months from the endoscopic confirmation of healing. • Extra surgery n=1/8
What are the limitations of this evidence?	The principal limitation is the small number of patients.
How was the study funded?	No funding or conflicts of interest declared.

Shalby et al 2019 Systematic review of endoluminal vacuum-assisted therapy as salvage treatment for rectal anastomotic leakage	
What are main differences in resource use and clinical outcomes between the technologies	Non comparative
How are the findings relevant to the decision problem?	A systematic review of relevant papers using Endo-SPONGE for treatment of colorectal anastomotic leak, demonstrating overall success of 83% of leak closure and 76% stoma closure rate in 276 patients
Does this evidence support any of the claimed benefits for the technology? If so, which?	• Demonstrates Endo-SPONGE is a safe and highly efficient approach to treat colorectal anastomotic leaks, N=228/276 (82.6%) patients healed with endoscopic vacuum therapy. Random-effects meta-analysis showed that the weighted mean success rate of EVT was 85·3 (95 % CI 80·1 to 90·5) % (I^2 =39·7 %) P=0.047. Compared with the current literature, which reports a stoma reversal rate of 30–40 % for clinical leakage, the weighted mean rate of stoma reversal across the studies was 75·9 %. • Endo-SPONGE can prevent need for long term stoma/ restore bowel continuity. N=107/141 underwent reversal of stoma following successful treatment. Random-effects meta-analysis showed the weighted mean rate of stoma reversal across the studies to be 75·9 (95 % CI 64·6 to 87·2) % (I^2 =72·7 %) P<0.001. • EVT has a good safety profile with a mean complication rate of approximately 14 %. Stenosis is the most common complication, and may be caused by anastomotic leakage rather than by EVT.
What cost analysis was done in the study? Please explain the results.	• None
Will any information from this study be used in the economic model?	• No to prevent duplication of results from primary sources
What are the limitations of this evidence?	This review has a number of limitations related to the available literature. These include small sample size. The design of most studies was retrospective. Despite the moderate statistical heterogeneity among studies, clinical heterogeneity was significant, including methods, indications and timing. It is therefore not possible to compare these studies on all endpoints. Long-term oncological and functional outcomes are awaited.
How was the study funded?	No funding or conflicts of interest declared

Srinivasamurthy et al 2013 An initial experience using transanal vacuum therapy in pelvic anastomotic leakage	
What are main differences in resource use and clinical outcomes between the technologies?	Non comparative
How are the findings relevant to the decision problem?	Paper demonstrates that initial treatment of colorectal anastomotic leakage with Endo-SPONGE is successful (75%) in n=8 patients with 62.5% stoma reversal.
Does this evidence support any of the claimed benefits for the technology? If so, which?	• Demonstrates Endo-SPONGE is a safe and highly efficient approach to treat colorectal anastomotic leakage. Complete closure N=6/8 (75%), low complication n=1/8 misplaced sponge, n=0/8 30 day mortality. • Endo-SPONGE can prevent need for long term stoma/ restore bowel continuity. Ileostomies reversed and "good function" N=5/8 (N=5 started Endo-SPONGE < 6 weeks, n=4/5 (80%) achieved bowel restoration with good results, N=3 started Endo-SPONGE treatment > 6 weeks, n=1/3 (33%) achieved bowel restoration with good results) • Treatment was well tolerated, n=1 patient complained of discomfort, but the device remained in situ. • Demonstrates low need for extra surgery N=2/8
What cost analysis was done in the study? Please explain the results.	• None
Will any information from this study be used in the economic model?	• Complete closure or reduction in size of abscess N=6/8. • Ileostomies reversed and "good function" N=5/8. • Median number of sponge applications was 4 (range 1–7), over a median treatment period of 26 days (range 7–49 days). • Extra surgery required for N=2/8
What are the limitations of this evidence?	• It was uncontrolled and cannot rule out that some fistula would have closed without Endo-SPONGE treatment. • It is a retrospective study in which only patients who were treated by Endo-SPONGE have been included. • Small sample size.
How was the study funded?	No funding or conflicts of interest declared

Strangio et al 2015 Endo-SPONGE therapy for management of anastomotic leakages after colorectal surgery: A case series and review of literature	
What are main differences in resource use and clinical outcomes between the technologies?	Non comparative
How are the findings relevant to the decision problem?	Paper demonstrates that initial treatment of colorectal anastomotic with Endo-SPONGE is successful (88%) in n=25 patients.
Does this evidence support any of the claimed benefits for the technology? If so, which?	• Demonstrates Endo-SPONGE is a safe and highly efficient approach to treat colorectal anastomotic leakage, N= 22/25 (88%) patient fully healed anastomotic leakage with sole use of Endo-SPONGE. No abscess recurrence in all 22 healed patients. N = 0/25 30 day mortality rate, and long term mortality rate of 3/12. • Low complication rate n=3/25 (12%) developed complications • Demonstrate Endo-SPONGE short treatment duration Treatment duration of 4 weeks (range 1–32). • Treatment was well tolerated, all patients well tolerated Endo-SPONGE permanence during the treatment interval. • Demonstrates low need for extra surgery following Endo-SPONGE (n=2/25)
What cost analysis was done in the study? Please explain the results.	• None
Will any information from this study be used in the economic model?	• N= 22/25 (88%) patient fully healed anastomotic leakage with sole use of Endo-SPONGE. • The median number of applications per patient was 9 (1–39 applications). • Extra surgery rate of 2/25 (8%)
What are the limitations of this evidence?	Lack of detailed background information of patients in case series available in tabulated form. Mixed study combining literature review with primary data.
How was the study funded?	No funding or conflicts of interest declared.

Van Koperen et al 2009 The Dutch multicentre experience of the Endo-SPONGE treatment for anastomotic leakage after colorectal surgery	
What are main differences in resource use and clinical outcomes between the technologies?	Non comparative
How are the findings relevant to the decision problem?	Paper demonstrates that initial treatment of colorectal anastomotic leakage with Endo-SPONGE is successful (56%) in n=16 patients.
Does this evidence support any of the claimed benefits for the technology? If so, which?	• Demonstrates Endo-SPONGE is a safe and highly efficient approach to treat colorectal anastomotic leakage. Overall leak closure, N=9/16 (56%), leak closure when treatment start <6 weeks n=6/8 (75%) and when treatment start >6 weeks n=3/8 (38%) P=0.315 between treatment start times and success. Low complications n=4/16, 30 day mortality rate of 0/16. • Endo-SPONGE can prevent need for long term stoma/ restore bowel continuity, stoma closure in 5/9 patients (56%). • Demonstrate Endo-SPONGE short treatment duration, median time to closure 40 days (28-90). • Demonstrates low need for extra surgery n=2/16
What cost analysis was done in the study? Please explain the results.	• None
Will any information from this study be used in the economic model?	• Overall success rate N=9/16 (56%). • Stoma closure in 5/9 patients (56%). • Time to closure 40 days (28-90). • Number of sponge exchanges 13 (8-17). • Need for extra surgery n=2/16
What are the limitations of this evidence?	• It was uncontrolled and cannot rule out that some fistula would have closed without Endo-SPONGE treatment. • Only patients who were treated by Endo-SPONGE have been included. • Being a prospective analysis, subjects were not randomized to closure cohorts. Nevertheless the baseline characteristics of the patients are displayed and no difference existed in respect to indication for surgery, type of surgery • Small sample size.
How was the study funded?	No funding or conflicts of interest declared

Weidenhagen et al 2008 Endoscopic vacuum-assisted closure of anastomotic leakage following anterior resection of the rectum: a new method.	
What are main differences in resource use and clinical outcomes between the technologies?	Non comparative
How are the findings relevant to the decision problem?	Paper demonstrates that initial treatment of colorectal anastomotic leakage with Endo-SPONGE is successful (96.5%) in n=29 patients.
Does this evidence support any of the claimed benefits for the technology? If so, which?	• Demonstrates Endo-SPONGE is a safe and highly efficient approach to treat colorectal anastomotic leakage, N=28/29 leaks healed, low complications n=3/34, 30 day mortality rate 1.34 (fell out of bed and cranial injury) • Endo-SPONGE can prevent need for long term stoma/ restore bowel continuity, n=22/25 of protecting stomas closed. • Reduce length of time with stoma, stoma reversed in a mean of 168.9 ± 81.7 days (range 9-321 days). • Demonstrates Endo-SPONGE short treatment duration, duration of endovac therapy 34.4 ± 19.4 days (range 4–79 days). • Endo-SPONGE changes care from secondary to community care n=25/29 (86.2%) patients therapy was continued as an ambulatory treatment. • Treatment was well tolerated. • None of the patients reported increase in pain and as reported by the patients, odour due to abscess was significantly better in 24 hours. • Demonstrates low need for extra surgery.
What cost analysis was done in the study? Please explain the results.	• None
Will any information from this study be used in the economic model?	• n=22/25 of protecting stomas closed during study in 168.9 ± 81.7 days (range 9-321 days). • Duration of Endovac therapy 34.4 ± 19.4 days (range 4–79 days). • Number of endoscopic sessions 11.4 ± 6.3 (range 1–27). • Duration of postoperative stay 10-69 days mean 30.5 ± 12.8. • In 25 of 29 patients therapy was continued as an ambulatory treatment. • Need for extra surgery 5/34
What are the limitations of this evidence?	• It was uncontrolled and cannot rule out that some fistula would have closed without Endo-SPONGE treatment. • It is a retrospective study in which only patients who were treated by Endo-SPONGE have been included. • Small sample size.
How was the study funded?	No funding or conflicts of interest declared.

4 Economic model

This section refers to the de novo economic model that you have submitted.

Description

Patients

Describe which patient groups are included in the model.

Patients with anastomotic leak following colorectal surgery. Leaks of all grades included.

Technology and comparator(s)

State the technology and comparators used in the model. Provide a justification if the comparator used in the model is different to that in the scope.

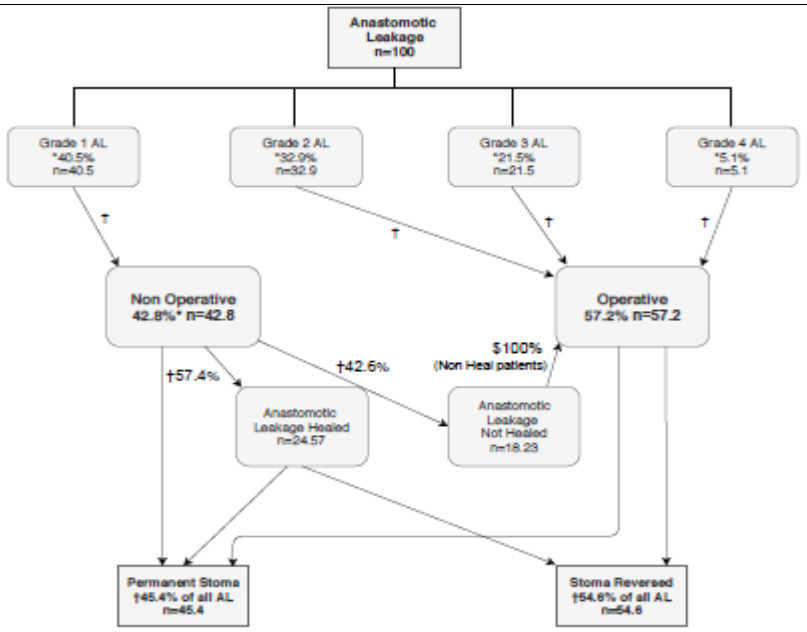
Technology – Endo-SPONGE Comparator – Current treatment pathway of non-operative means (Percutaneous drain) or operative interventions

Model structure

Provide a diagram of the model structure you have chosen in Appendix C.

Justify the chosen structure of the model by referring to the clinical care pathway outlined in part 1, section 3 (Clinical context) of your submission.

We have chosen two decisions trees, current AL pathway and Endo-SPONGE pathway, as we want to compare two different care pathways. We also want to compare costs of these two pathways and have created a budget impact model to examine the impact of implementing the Endo-SPONGE pathway in comparison to the current AL care pathway. We believe this is the best way to compare the two alternatives. A decision tree was required for current care as there is no standard treatment pathway for AL and the data from the AL meta-analysis was used to map out as accurately as possible the current AL treatment pathway.

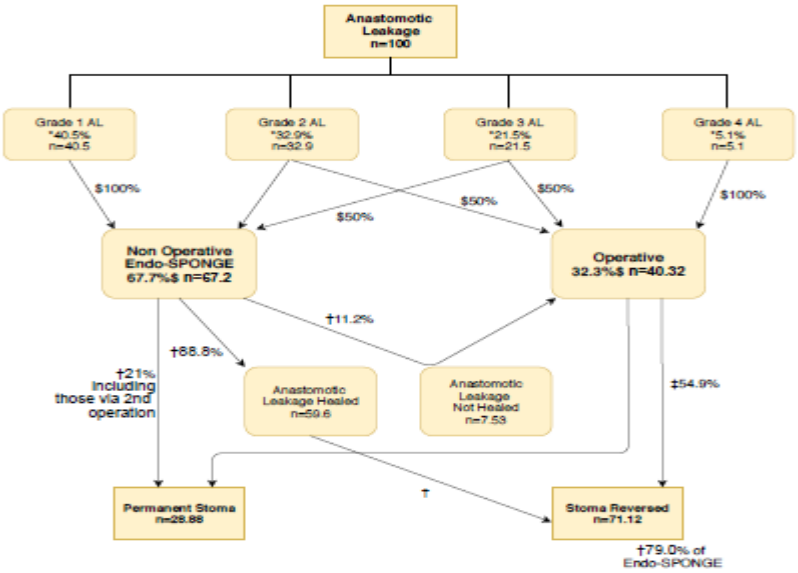


* = Asteria et al.

$ = Assumption.

† = Meta-analysis.

Note: Stoma reversal figure of 52.7% on ALL current AL patients, irrespective of treatment.



* = Asteria et al.

$ = Assumption.

† = Meta-analysis.

‡ = Current AL data.

Table 2 Assumptions in the model

In this table, list the main assumptions in the model and justify why each has been used.

Assumption	Justification	Source
Calculations based on 100 AL patients	Easy number to manipulate	N/A
40.5% of leaks are grade 1, 32% of leaks are grade 2, 21.5% of leaks are grade 3 and 5.1 % of leaks are grade 4	Reported in literature by Asteria et al 2008.	Asteria et al 2008
In current AL treatment pathway, Assumed all grade 1 leaks will be treated with non operatively treatments and all grade, 2,3 and 4 leaks will be treated operatively	Meta-analysis of current AL pathway demonstrated 42.8% of AL patients were treated non-operatively. This is very close to the 40.5% allocated to grade 1 to account for all grade 1 leaks	Current AL pathway meta-analysis page 12
In Endo-SPONGE pathway Assume ALL grade 1 leaks are treated non-operatively. Assume grade 2 and 3 leaks, 50% of leaks are treated non-operatively and 50% are treated operatively. Assume all Grade 4 leaks are treated operatively	The association of great Britain and Ireland grade AL's 1-5 (F D McDermott et al. 2016). Grade 1, no sepsis, Grade 2a Sepsis with contained leak/abscess <3 cm, Grade 2b Sepsis with contained leak/abscess> 3cm, Grade 3 Sepsis, ileus single quadrant peritonitis , Grade 4 Severe sepsis, more than 1 quadrant peritonitis, and Grade 5 Septic shock, generalised peritonitis. From these definitions AL's grade 1-2b would be applicable (patient dependant) for treatment with Endo-SPONGE, as per the individual surgeon's medical consideration of the whole patient health status. Asteria et al 2008 classify AL's 1-4 (grade 1 Limited leakage with small adjacent abscess; mild clinical signs (40.5%), grade 2 Small lateral anastomotic failure with adjacent unilocular abscess (approximately 5 cm diameter or greater) (32.9%) grade 3 Failure of half or more of the circumference of an anastomosis (21.5%) and grade 4 Multiocular abscess or peritonitis (5.1%). Frome these	McDermott et al 2016 Asteria et al 2008

	definitions all grade 1 and some grade 2 and 3 would be suitable for Endo-SPONGE treatment.	
ALL leaks failing to heal following non operative treatment (current pathway or Endo-SPONGE pathway) will require treatment by operative means	Non healed AL will require surgery if non-operative treatment did not work. Meta-analysis for Endo-SPONGE demonstrated the same number of treatment failures as secondary operative treatments.	Meta-analysis for Endo-SPONGE
Assume out of 100 patients in the current AL pathway 75.433 will require a re-operation	57.2 patients will have a re-operation as initial solution to AL. Of the 42.8 patients treated non-operatively, 18.23 leak will not heal and will require secondary surgery to resolve AL. Total 75.433 patients requiring re-operation in current AL pathway	Meta-analysis and Current AL pathway model page 12
Assume out of 100 patients 40.326 in the Endo-SPONGE treatment will require re-operation	Based on assumption above that 67.2% of patients on Endo-SPONGE pathway will be treated non-operatively then, 42.6% (32.8 patients) will have a re-operation as initial solution to AL. Of the 67.2 patients treated with Endo-SPONGE, 11.2 % (7.526 leaks) will not heal and will require secondary surgery to resolve AL. Total 39.882 patients requiring re-operation in Endo-SPONGE pathway	Meta-analysis and Endo-SPONGE pathway model page 13.
Number of re-operations saved with Endo-SPONGE versus current AL pathway = 33.352 per 100 patients	75.433 re-operations with current AL pathway minus 40.326 re-operations with Endo-SPONGE pathway = 35.550. Based on calculations above.	Meta-analysis and Current AL pathway model page 12 Meta-analysis and Endo-SPONGE pathway model page 13.
Cost of re-operation £12,594.34	Based on assumptions below	See below
Length of re-surgery assumed at 4.5 hours	Four hours was the most commonly planned duration for a scheduled theatre session (34%), followed by 3½ hours (16%), 8 hours (10%), 9 hours (8%) and 8½ hours (7%). But there was wide variation in durations between the eight highest volume surgical specialties	https://improvement.nhs.uk/documents/3711/Theatre_productivity_report__Final.pdf
Cost of operating theatre of £5,400 for 4.5 hours	Running costs of an operating theatre reported to average £1,200 per hour	http://harmfreecare.org/wp-content/files_mf/Improving-

		quality-and-efficiency-in-the-operating-theatre.pdf
1x Consultant surgeon required at a cost of £486 for 4.5 hours	Consultant surgeon, £108 cost per working hour.	https://www.pssru.ac.uk/pub/uc/uc2018/hospital-based-health-care-staff.pdf
1x Anaesthetist average cost of £384.00 for 4.5 hours	Anaesthetist Registrar, £43 per working hour Anaesthetist Associate specialist, £105 per working hour Consultant Anaesthetist, £108 per working hour Average, £85.33 per working hour	https://www.pssru.ac.uk/pub/uc/uc2018/hospital-based-health-care-staff.pdf
2 x Scrub nurse average cost of £184.50 each for 4.5 hours	Band 5 Nurse cost per working hour, £37.00 per hour and Band 6 Nurse £45.00 per hour. Average £41.00 cost per working hour	https://www.pssru.ac.uk/pub/uc/uc2018/hospital-based-health-care-staff.pdf
Theatre support cost of £99.00 for 4.5 hours	Band 2 £22.00 per working hour hour	https://www.pssru.ac.uk/pub/uc/uc2018/hospital-based-health-care-staff.pdf
Increased bed stay of 14.18 days	Meta-analysis = bed stay no AL 11.33 days, Bed stay with AL 25.51 days, difference 14.18 days	Meta-analysis page 18
Cost of increased bed stay £5,856.34	Bed stay cost of £413.00 per day for 14.18 days	http://www.wales.nhs.uk/documents/delivery-plan-for-the-critically-ill.pdf
Stoma NOT reversed current AL pathway 44.5% of patients	Meta-analysis of Current AL pathway	Meta-analysis of Current AL pathway page 14

Stoma NOT reversed Endo-SPONGE pathway total 29.63 patients out of 100 of patients	21% of Endo-SPONGE treated patients (n=67.2 Endo-SPONGE treated patients) and 47.3% of patient initially treated with an operation (n=32.8 patients) = 29.63 patients out of 100 initial patients. Meta-analysis of Endo-SPONGE pathway	Meta-analysis of Endo-Sponge pathway page 14 &15.
Number of permanent stomas saved with Endo-SPONGE pathway compared with current AL pathway, 18.41 per 100 patients	47.30 permanent stoma with current AL pathway minus 29.63 permanent stoma with Endo-SPONGE pathway. Calculation from above.	Meta-analysis and Current AL pathway model. Meta-analysis and Endo-SPONGE pathway model.
Annual cost of stoma care per patient per year [redacted]	See below for break down	See below and Excel file Overall estimated stoma cost_pt_year
Average number of stoma patients in UK = 118,649	Reported 102,000 people with stoma in UK 1 in 500 patients have a stoma in UK = 135298, based on 67,640,000 UK population	Stoma care: the market in products lets patients down. https://www.ncbi.nlm.nih.gov/pubmed/24136685 http://www.colostomyuk.org/information/what-is-a-stoma/ Overall estimated stoma cost_pt_yearxlsx .
Average cost of stoma care [redacted] **per patient per year**	Tableau data Mar 2018-Feb 2019 [redacted] spent on stoma and base plates. Cost per patient [redacted]	Tableau Data – Stoma Care xlsx
Prescription cost analysis (PCA), other Dispensing Applying Contractor (DAC) fees	Based on the NHS Business Services document for NHS prescription services NHS DAC data [redacted] for Jan-June 2019 – forecast for year 2019 at [redacted]. Mean cost per patient calculated at [redacted]	https://www.nhsbsa.nhs.uk/sites/default/files/2019-05/Understanding%20your%20schedule%20of%20payments%20-%20PEPS%20opt-in%20contractor.pdf PCA Data-OtherDAC's 2019 xlsx

PCA other stoma accessories [redacted] per patient per year	PCA data for stoma accessories for Jan-March 2019 [redacted] Year estimate at [redacted]	Jan-March 2019 PCA Data-Stoma accessories
Cost per single Endo-Sponge and drain £271.11	Endo-SPONGE pack of 10 = £2,502.39 Endo-SPONGE vacuum bottle pack of 10 £208.72	B Braun list price
Cost to insert Endo-SPONGE £402.66	See details below	See details below
Time to insert Endo-SPONGE 15 minutes	Time taken to insert Endo-SPONGE 15 minutes (range 5-65)	(Arezzo et al. 2015b) (Riss et al. 2009)
Endoscopy Unit at £94.30 per procedure	Approximately 530,000 endoscopies are performed each year at a cost to the NHS of £50 million. £50 million / 530,000= £94.30 per endoscopic procedure	https://www.bsg.org.uk/asset/1F45A93B-ACB6-468D-A92AD6C3F0AB0658
1 x Consultant surgeon £27.00 for 15 Minutes	Consultant surgeon, £108 cost per working hour.	https://www.pssru.ac.uk/pub/uc/uc2018/hospital-based-health-care-staff.pdf
1 x Nurse for 15 minutes £10.25	Band 5 Nurse cost per working hour, £37.00 per hour and Band 6 Nurse £45.00 per hour. Average £41.00 cost per working hour	https://www.pssru.ac.uk/pub/uc/uc2018/hospital-based-health-care-staff.pdf
Cost of Inserting percutaneous drain £182.95	See details below	See details below
Insertion time 20 minutes for percutaneous drain	20 minutes can be up to 90 minutes	http://www.wales.nhs.uk/sitesplus/documents/866/PIU431%284%29%28ABUHB%29%28Active%29%28JAN%2017%29.pdf
Cost for X-Ray department for 20 Minutes £99.00	Chest x-ray (5 Min) cost £25 = £300 per hour for X-ray department	https://docs.google.com/spreadsheets/d/1IlwMM6ECI0KKgzeA6Ku32ReSz6O9RYNP-uaCbJIsJhI/edit#gid=0

1x Radiologist average cost of £28.16 for 20 minutes	Anaesthetist Registrar, £43 per working hour Anaesthetist Associate specialist, £105 per working hour Consultant Anaesthetist, £108 per working hour Average, £85.33 per working hour	https://www.pssru.ac.uk/pub/uc/uc2018/hospital-based-health-care-staff.pdf
1 x Nurse for 20 minutes £13.53	Band 5 Nurse cost per working hour, £37.00 per hour and Band 6 Nurse £45.00 per hour. Average £41.00 cost per working hour	https://www.pssru.ac.uk/pub/uc/uc2018/hospital-based-health-care-staff.pdf
Average unit cost of percutaneous drain	Range of 99 drains sourced from NHS SC catalogue	See copy of percutaneous drain xls
Assume LOS for Percutaneous treatment and Endo-SPONGE treatment is the same	Both minimally invasive treatments	N/A

Table 3 Clinical parameters, patient and carer outcomes and system outcomes used in the model

In this table, describe the clinical parameters, patient and carer outcomes and system outcomes used in the model.

Parameter/outcomes	Source	Relevant results	Range or distribution	How are these values used in the model?
Anastomotic Leak severity and patient split	Asteria et al 2008	Grade 1 40.5% Grade 2 32.9% Grade 3 21.5% Grade 4 5.1%	Text	Used to determine number of patients suitable for non – operative means of treatment
Stoma reversal rate	Meta-analysis section 2 page 14	Non operative current treatment stoma reversal rate 54.5% Endo-SPONGE success 79.0%	95% CI 46.0 to 63.0% 95% CI 71.9 to 86.1	Demonstrate cost impact to system. Not discussed in model but impact on patients quality of life with having a permanent stoma to be considered. Impact of stoma care on addition NHS visits and complications NOT included
Non-operative treatment (percutaneous drain or Endo-SPONGE) success rate	Meta-analysis section 2 page 13-14	Non operative success rate current AL treatment 57.4% Endo-SPONGE success rate 88.8%	95% CI 41.8 to 72.9% 95% CI 85.2 to 92.4	Demonstrate accurate number of patients who will be operated on. Those initially treated via operation and those whose non operative treatment failed.
LOS	Meta-analysis &	Increased by 14.18 days following re-operation		

If any outcomes listed in table 4 are extrapolated beyond the study follow-up periods, explain the assumptions that underpin this extrapolation.

N/A No extrapolation has been included

Table 4 Other parameters in the model

Describe any other parameters in the model. Examples are provided in the table. You can adapt the parameters as needed.

Parameter	Description	Justification	Source
Time horizon	10 years	Longitudinal demonstration of care for patients	Text
Perspective (NHS/PSS)	NHS	NHS is primary consumer	B Braun
Cycle length	1 year	Calendar year	Text

Explain the transition matrix used in the model and the transformation of clinical outcomes, health states or other details.

This model does not underlie a classic transition matrix. Two different treatment pathways are compared, Endo-Sponge vs. current treatment. The patient follows the pathways and the possible different outcomes like heal or non-heal. Every branch of our pathway is attached with a probability that the patient follows that way. The probabilities underlie literature and come from the meta-analysis above. (see Section 2)

Resource identification, measurement and valuation

Technology costs

Provide the list price for the technology (excluding VAT).

Endo-SPONGE pack of 10 £2,502.39 excl VAT Redyrob Trans plus pack of 10 £208.72 excl VAT

If the list price is not used in the model, provide the price used and a justification for the difference.

N/A

NHS and unit costs

Describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs, the national tariff and unit costs (from PSSRU and HSCIC). Please provide relevant codes and values (e.g. OPCS codes and ICD codes) for the operations, procedures and interventions included in the model.

There are no ICD10 codes within HES data to identify for anastomotic leak (Ashraf et al. 2013)

No national tariff codes were included in the model, below are a list of potential tariff codes which could be attributed to anastomotic leak treatment.

Currency codes	Description
FZ10A	Distal colon procedures with major complications
FZ10B	Distal colon procedures without major complications
FZ12A	General Abdominal - Very Major or Major Procedures with major complications
FZ27A	Endoscopic or Intermediate General Abdominal Procedures
FZ17A	Abdominal Hernia Procedures with major complications
GB04C	Endoscopic/Radiology category 1 without complications
XC05Z	Adult Critical Care - 2 Organs Supported
XC06Z	Adult Critical Care - 1 Organs Supported
RA12Z	Computerised Tomography Scan, two areas with contrast
K914	Colostomy malfunction
Z433	Attention to colostomy
Z432	Attention to ileostomy
FZ62A	Endoscopic or intermediate, lower GI tract procedures
FE30Z	Therapeutic colonoscopy
FE31Z	Diagnostic colonoscopy with biopsy
FE32Z	Diagnostic colonoscopy
FF33A	Distal Colon Procedures with CC score 3+
FF33B	Distal Colon Procedures with CC score 0
WH07A	Infections or Other Complications of Procedures, with Multiple Interventions, with CC Score 2+
WH07B	Infections or Other Complications of Procedures, with Multiple Interventions, with CC Score 0-1
WH07C	Infections or Other Complications of Procedures, with Single Intervention, with CC Score 2+
WH07D	Infections or Other Complications of Procedures, with Single Intervention, with CC Score 0-1
WH07E	Infections or Other Complications of Procedures, without Interventions, with CC Score 4+
WH07F	Infections or Other Complications of Procedures, without Interventions, with CC Score 2-3
WH07G	Infections or Other Complications of Procedures, without Interventions, with CC Score 0-1
FD01F	Gastrointestinal Infections without Interventions, with CC Score 8+
FD01G	Gastrointestinal Infections without Interventions, with CC Score 5-7
FD01H	Gastrointestinal Infections without Interventions, with CC Score 2-4
FD01J	Gastrointestinal Infections without Interventions, with CC Score 0-1

FD03G	Gastrointestinal Bleed without Interventions, with CC Score 5-8
FD03H	Gastrointestinal Bleed without Interventions, with CC Score 0-4

Resource use

Describe any relevant resource data for the NHS in England reported in published and unpublished studies. Provide sources and rationale if relevant. If a literature search was done to identify evidence for resource use then please provide details in appendix D.

Prescription cost analysis (PCA) data - stoma accessories cost (supplementary Excel file PCA Data-stoma Acessoriesxlsx)
PCA data – DAC's (supplementary Excel file PCA Data-others DAC's2019xlsx)
https://www.nhsbsa.nhs.uk/prescription-data/dispensing-data/prescription-cost-analysis-pca-data
Tableau data – stoma care costs, sourced via Inspiremed (supplementary Excel file Tableau Data stoma care xlsx)
HES data sourced via vantage
PRSSU – healthcare hourly costs
https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2018/

Literature search - AL and economics (appendix D)

(Ashraf et al. 2013)

- AL resulted in an average increase of £3,372 to £10,901 in the cost of a hospital episode.
- A significant cost difference between those managed conservatively (DH index cost data: £9686 ± £2626) and those undergoing laparotomy(DH index cost data: £20671 ± £11301) (P = 0.0012; Mann–Whitney U-test)
- Annual cost of elective ARs £18 225 292 to £18 476 756 (number of ARs x average cost of procedure = 2924 x £6233 (HRG cost) or £6319 (DH cost)).
- Using Oxford AL rate (10.9%), the additional annual hospital cost incurred is estimated to be £1074710 to £3474323 (number of ARs x frequency of ALs x average incremental cost attributed to AL = 2924 x 0.109 x £3372 (HRG incremental 'leakage' cost) or £10 901 (DH incremental 'leakage' cost)).
- The majority (83.3%) of this additional cost actually arises in the subgroup of ALs that require laparotomy and stoma formation ([2924 x 0.056 x £5468 (HRG incremental 'severe leakage' cost) or £14 352 (DH incremental 'severe leakage' cost)] =£895352 to £2 350054).

(Lasithiotakis, Aghahoseini, and Alexander 2016)
(Lasithiotakis, Aghahoseini, and Alexander 2016)

- Stoma cost, late closure group (median 57 days IQR 38 days) median £311 (IQR £108)

Describe the resources needed to implement the technology in the NHS. Please provide sources and rationale.

Anastomotic leaks occur in just under 10% of all anastomoses following colorectal surgery.

Lead time from hospital order to delivery of product is 24-48 hours depending on time of order.

In order for patients to benefit as soon as possible from early use of Endo-SPONGE it is advisable for hospitals, performing colorectal surgery, to stock 1 pack each of 10 Endo-SPONGE and 1 pack of 10 Redyrob negative pressure bottle kits.

From an NHS standpoint, the resource required would include the colorectal/endoscopy MDT team trained on how to effectively administer the Endo-SPONGE treatment, they should also be aware of the different leak severities and know when to use Endo-SPONGE and when not, this may require.

The Endo-SPONGE technology and the overall treatment have quite a short learning curve, especially for clinicians with endoscope experience, there may be some training required for registrars or new consultants, but this is often done internally by more senior clinicians.

If the technology was to be implemented in every NHS site we would have to decide on a training plan to make sure that every site is given the required training and expertise to deliver the treatment effectively.

Describe the resources needed to manage the change in patient outcomes after implementing the technology. Please provide sources and rationale.

To make the treatment successful (especially when patients are going home) the treatment would have to be talked through and the would need to know about the tube coming from the anus and connecting to the bottle to make sure they don't disconnect it or turn it off. Attached is the patient brochure to be discussed by staff and given to patients.

Describe the resources needed to manage the change in system outcomes after implementing the technology. Please provide sources and rationale.

Patients would require the treatment to be changed every 2-3 days, the system would need enough trained personnel to cover the sponge changes regularly, and this would usually require a nurse and consultant surgeon/endoscopist. To do the changes every 2-3 days they would need a slot in the endoscopy suite or theatres. If done in the endoscopy suite, the treatment would take around 20 mins, it may be longer in a theatre environment.

Table 5 Resource use costs

In this table, summarise how the model calculates the results of these changes in resource use. Please adapt the table as necessary.

RESOURCE COST

Cost of Endo-SPONGE INSERTION				
Resource required	**Average hourly cost**	**Time required (hours)**	**Number required**	**Total cost per treatment**
Nurse	£41.00	0.25	1	£10.25
Consultant Surgeon	£108.00	0.25	1	£27.00
Endoscopy Unit		0.25	1	£94.30
Endo-SPONGE	N/A	N/A	1	£250.24
Redyrob bottle	N/A	N/A	1	£20.87
Endo-SPONGE insertion cost per insertion				**£402.66**
Average number of treatments overall per patient			10.7	
Total cost per course of Endo-SPONGE treatment				**£4,308.46**

Cost of Percutaneous Drain INSERTION				
Resource required	**Average hourly cost**	**Time required (hours)**	**Number required**	**Total cost per treatment**
Nurse	£41.00	0.33	1	£13.53
Radiologist	£85.33	0.33	1	£28.16
X-ray/CT Department	£300.00	0.33	1	£99.00
Percutaneous drain and bottle	N/A	N/A	1	[redacted]
Total Percutaneous insertion costs per insertion				**£182.95**
Average Number of treatments overall per patient			4.4	
Total cost per course of Percutaneous drain treatment				**£804.98**

Difference in cost per treatment course of Endo-SPONGE / patient over percutaneous drain	**£3,503.48**

Cost of re-operation				
Resource required	**Average hourly cost**	**Time required (hours)**	**Number required**	**Total cost per treatment**
Nurse	£41.00	4.5	2	£369.00
Theatre support	£22.00	4.5	1	£99.00
Anaesthetist	£85.33	4.5	1	£384.00
Consultant Surgeon	£108.00	4.5	1	£486.00
Theatres	£1,200.00	4.5	1	£5,400.00
Hospital Bed	£413.00 (per DAY)	14.18 (DAYS)	1	£5,856.34
TOTAL re-operation and bed stay cost per patient				**£12,594.34**

Re-operation cost per 100 patient per pathway		
Number of Patient re-operation per 100 patients		**Total Costs per 100 Patients**
Endo-SPONGE pathway	39.882	£502,292.51
Current Pathway	75.433	£950,026.33
Cost difference in re-operation cost for Endo-SPONGE pathway versus current pathway		**-£447,733.82**

* Negative values indicate a cost saving.

OUTCOME COSTS

Cost of permanent stomas		
Annual cost per stoma/patient		[redacted]
Number of patients permanent stoma per 100 patients		**Total annual cost**
Endo-SPONGE	28.88	£89,950.50
Current pathway	45.40	£141,389.30
Cost difference in permanent stoma cost for Endo-SPONGE versus current pathway		**-£51,447.80**

Adverse event costs

If costs of adverse events were included in the analysis, explain how and why the risk of each adverse event was calculated.

Treatment failure of non –operative treatments were the only adverse events included in the pathway

Table 6 Adverse events and costs in the model

In this table, summarise the costs associated with each adverse event included in the model. Include all adverse events and complication costs, both during and after long-term use of the technology. Please explain whether costs are provided per patient or per event.

Adverse event	Items	Cost	Source
Treatment failure – conversion to re-operative treatment	Technology	N/A	Text
	Staff	£1,338.00	PRSSU https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2018/
	Theatre costs	£5,400.00	http://harmfreecare.org/wp-content/files_mf/Improving-quality-and-efficiency-in-the-operating-theatre.pdf
	Extra LOS	£5,856.34	http://www.wales.nhs.uk/documents/delivery-plan-for-the-critically-ill.pdf
	Total	£12,594.34	Text

Miscellaneous costs

Describe any additional costs or resource considerations that have not been included elsewhere (for example, PSS costs, and patient and carer costs). If none, please state.

Frequency of stoma problems and costs (hernias, re-admissions associated with stoma etc.)
Costs of sepsis for any AL
Costs of antibiotic use

Are there any other opportunities for resource savings or redirection of resources that have not been possible to quantify?

Reduced antibiotic use - antibiotics use in current AL pathway measured at 51.5% of patients and reduced to 26.7% when prescribed before or during Endo-SPONGE treatment and reduced further to 10.9% when clinicians decide to introduce antibiotics based on patient needs rather than study protocol. (http://www.wales.nhs.uk/sitesplus/documents/866/PIU431%284%29%28ABUHB%29%28Active%29%28JAN%2017%29.pdf)

Reduction in stoma complications (blockage, hernia, infection, bleeding, stoma fistula, stoma retraction, stoma stricture, leakage and prolapse)

Reduction in 30d mortality
Reduction in mortality – patients treated with non-operational intervention have a significant decrease in mortality of patients (4.6% vs 7.9%; AOR, .14; P 5.04) Moghadamyeghaneh et al 2015. Use of Endo-SPONGE can reduce number of patients needing re-operation, reducing overall mortality of AL.

Improved rates of bowel continuity
Reduction in duration with stoma – shorter time to stoma reversal
Improved long term success rate
Reduction in nutrition support (enteral and TPN)
Reduction in ICU LOS
Reduction in treatment complications

Total costs

In the following tables, summarise the total costs:

- Summarise total costs for the technology in table 7.
- Summarise total costs for the comparator in table 8. This can only be completed if the comparator is another technology.

Table 7 Total costs for the technology in the model

Cost of Endo-SPONGE INSERTION					
Resource required	**Average hourly cost**	**Time required (hours)**	**Number required**	**Total cost per treatment**	**Source**
Nurse	£41.00	0.25	1	£10.25	PRSSU
Consultant Surgeon	£108.00	0.25	1	£27.00	PRSSU
Endoscopy Unit		0.25	1	£131.55	https://www.bsg.org.uk/asset/1F45A93B-ACB6-468D-A92AD6C3F0AB0658
Endo-SPONGE	N/A	N/A	1	£250.24	List Price
Redyrob bottle	N/A	N/A	1	£20.87	List Price
Consumables per year (if applicable) and over lifetime of device				N/A	N/A
Maintenance cost per year and over lifetime of device				N/A	N/A
Training cost over lifetime of device				N/A	N/A
Other costs per year and over lifetime of device				N/A	N/A
Endo-SPONGE insertion cost per insertion				**£402.66**	
Average number of treatments overall per patient			10.7		
Total cost per course of Endo-SPONGE treatment				**£4,308.46**	

Addition of operation cost included in Endo-SPONGE pathway for 40 patients per 100 with AL

Cost of re-operation					
Resource required	**Average hourly cost**	**Time required (hours)**	**Number required**	**Total cost per treatment**	**Source**
Nurse	£41.00	4.5	2	£369.00	PRSSU
Theatre support	£22.00	4.5	1	£99.00	PRSSU
Anaesthetist	£85.33	4.5	1	£384.00	PRSSU
Consultant Surgeon	£108.00	4.5	1	£486.00	PRSSU
Theatres	£1,200.00	4.5	1	£5,400.00	http://harmfreecare.org/wp-content/files_mf/Improving-quality-and-efficiency-in-the-operating-theatre.pdf
Hospital Bed	£413.00 (per DAY)	14.18 (DAYS)	1	£5,856.34	http://www.wales.nhs.uk/documents/delivery-plan-for-the-critically-ill.pdf
TOTAL re-operation and bed stay cost per patient				**£12,594.34**	

Table 8 Total costs for the comparator in the model

Cost of Percutaneous Drain INSERTION					
Resource required	**Average hourly cost**	**Time required (hours)**	**Number required**	**Total cost per treatment**	**Source**
Nurse	£41.00	0.33	1	£13.53	PRSSU
Radiologist	£85.33	0.33	1	£28.16	PRSSU
X-ray/CT Department	£300.00	0.33	1	£99.00	https://docs.google.com/spreadsheets/d/1IlwMM6ECI0KKgzeA6Ku32ReSz6O9RYNP-uaCbJIsJhI/edit#gid=0
Percutaneous drain and bottle	N/A	N/A	1	[redacted]	NHSSC – see spread sheet Percutaneous drains NHSSC
Consumables per year (if applicable) and over lifetime of device				N/A	N/A
Maintenance cost per year and over lifetime of device				N/A	N/A
Training cost over lifetime of device				N/A	N/A
Other costs per year and over lifetime of device				N/A	N/A
Total Percutaneous insertion costs per insertion				**£182.95**	
Average Number of treatments overall per patient			4.4		
Total cost per course of Percutaneous drain treatment				**£804.98**	

Addition of operation cost included in Endo-SPONGE pathway for 73.678 patients per 100 with AL

Cost of re-operation					
Resource required	**Average hourly cost**	**Time required (hours)**	**Number required**	**Total cost per treatment**	**Source**
Nurse	£41.00	4.5	2	£369.00	PRSSU
Theatre support	£22.00	4.5	1	£99.00	PRSSU
Anaesthetist	£85.33	4.5	1	£384.00	PRSSU
Consultant Surgeon	£108.00	4.5	1	£486.00	PRSSU
Theatres	£1,200.00	4.5	1	£5,400.00	http://harmfreecare.org/wp-content/files_mf/Improving-quality-and-efficiency-in-the-operating-theatre.pdf
Hospital Bed	£413.00 (per DAY)	14.18 (DAYS)	1	£5,856.34	http://www.wales.nhs.uk/documents/delivery-plan-for-the-critically-ill.pdf
TOTAL re-operation and bed stay cost per patient				**£12,594.34**	

Results

Table 9 Base-case results

In this table, report the results of the base-case analysis. Specify whether costs are provided per treatment or per year. Adapt the table as necessary to suit the cost model. If appropriate, describe costs by health state.

The displayed cost are per year calculated for 100 patients. The calculations assume the introduction of Endo Sponge and shows the cost differences of the two treatment pathways.

Number of OP per year under current treatment	Number of OP saved introducing Endo-Sponge	Cost of re-operation	OP cost impact Endo-Sponge per year	Number of permanent stoma saved per year under Endo-Sponge	Impact of Endo-SPONGE on permanent stoma cost	Additional investment to introduce Endo-Sponge over percutaneous drain / year	Overall Budget Impact introducing Endo-Sponge
75.433	35.550	£12.594,34	**-£ 447,733.82**	16.519	**-£ 51,447.80**	**£ 237,185.73**	**- £ 261,995.90**
* Negative values indicate a cost saving.							

Scenario analysis

If relevant, explain how scenario analyses were identified and done. Cross-reference your response to the decision problem in part 1, section 1 of the submission.

N/A

Describe the differences between the base case and each scenario analysis.

N/A

Describe how the scenario analyses were included in the cost analysis.

N/A

Describe the evidence that justifies including any scenario analyses.

N/A

Table 10 Scenario analyses results

In this table, describe the results of any scenario analyse that were done. Adapt the table as necessary.

	Mean discounted cost per patient using the technology (£)	Mean discounted cost per patient using the comparator (£)	Difference in cost per patient (£)*
Scenario 1 (total costs)	N/A	N/A	N/A
Scenario 2 (total costs)	N/A	N/A	N/A
* Negative values indicate a cost saving. Adapt this table as necessary.			

Sensitivity analysis

Describe what kinds of sensitivity analyses were done. If no sensitivity analyses have been done, please explain why.

In the first step we have chosen a **univariate sensitivity analysis**. We changed all variables having an impact on our model by +/-10%.
After that step we identified the 3 variables with the biggest impact and performed a **multivariate sensitivity analysis** with all 3 variables at a time changing either +10% or -10%.
After univariate sensitivity analysis it has turned out that the 3 variables with the major impact on the results are as follows:

- Patients OP Stage 1 Current Process
- Cost of re-operation
- Total cost to insert Endo-SPONGE per Session

We performed 2 scenarios in the multivariate sensitivity analysis:

1) For **Endo-SPONGE unfavourable** changes in variables:
- Patients OP Stage 1 Current Process -10%
- Cost of re-operation -10%
- Total cost to insert Endo-SPONGE per Session +10%

2) For **Endo-SPONGE favourable** changes in variables:
- Patients OP Stage 1 Current Process +10%
- Cost of re-operation +10%
- Total cost to insert Endo-SPONGE per Session -10%

Summarise the variables used in the sensitivity analyses and provide a justification for them. This may be easier to present in a table (adapt as necessary).

Please Note:
Sensitivity analysis has been performed through the scenario manager. Variables can be changed individually via this process. The results are summarised manually in “Budget Impact” spread sheet. All variables used in the spread sheet “op insertion cost” are automatically included in the sensitivity analysis, since the value “op insertion cost” is changed as one overall value. This is much stronger than changing every single variable. Changing only one variable from the spread sheet “op insertion cost” will have a minor impact compared to changing the overall value. By changing the value which will have the largest impact on the budget model the robustness of the model is demonstrated, as the results are still favorable when changing the overall value instead of “op insertion cost”.

We included all variables having an influence on the results of the budget impact model

- Patients OP Stage 1 Current Process
- Patients OP Stage 1 Endo-SPONGE Process
- NON OP fail rate return to OP Current Process
- NON OP fail rate return to OP Endo-SPONGE Process
- Cost of re-operation
- Permanent Stoma rate Current Process
- Permanent Soma rate Endo-SPONGE
- Annual cost of stoma
- Total cost to insert Endo-SPONGE per Session
- Weighted mean number of Sponges
- Cost of percutaneous drain per session

If any parameters or variables listed in table 3 were omitted from the sensitivity analysis, please explain why.

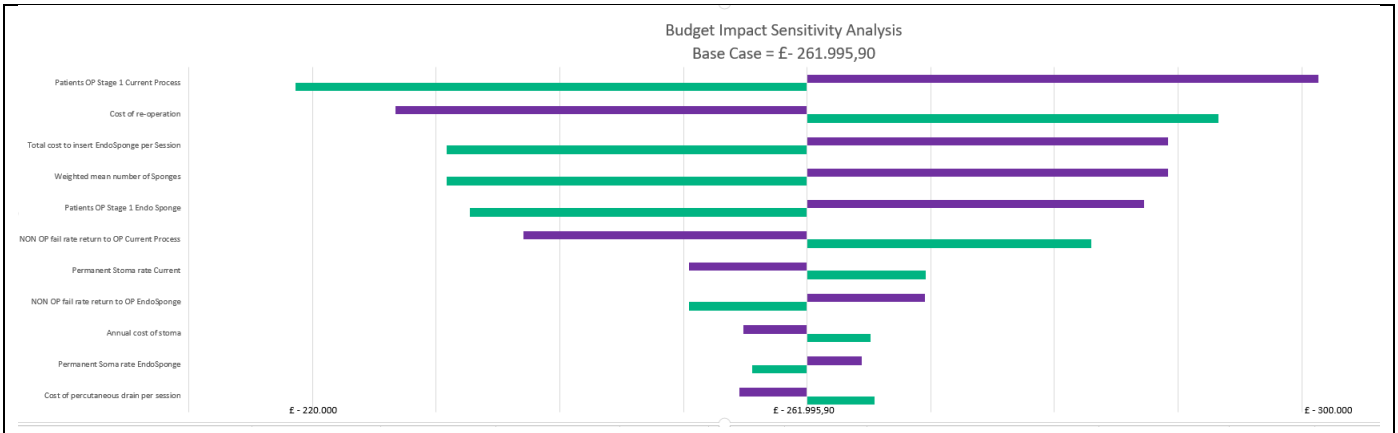
“Anastomotic Leak severity and patientt split“ is indirectly covered in the sensitivity analysis to group patients after AL grade into OP and non OP patients. In the analysis they are covered as “Patients OP Stage 1” and as the reciprocal

“Length of stay“ is indirectly covered as part of “cost of re-operation” (further calculations see spread sheet Budget Impact xlsx)

Sensitivity analyses results

Present the results of any sensitivity analyses using tornado plots when appropriate.

Univariate Sensitivity analysis:
Results are shown for Year 1 only, since the savings sum up over the years and get bigger.
The Base Case result was a saving in year 1 of £ 261.995,90. The tornado plot shows the results of the analysis:



Multivariate Sensitivity Analysis:

Even changing the 3 variables with the biggest impact on the result simultaneously in an unfavorable way for Endo-SPONGE leads to a saving of £ 161.293,10 in Year 1.

	Budget Impact Year 1
Cost of re-operation -10%	
Patients OP Stage 1 Current Process -10%	-£ 161.293,10
Total cost to insert EndoSponge per Session +10%	

	Budget Impact Year 1
Cost of re-operation +10%	
Patients OP Stage 1 Current Process +10%	-£ 381.423,39
Total cost to insert EndoSponge per Session -10%	

What were the main findings of each of the sensitivity analyses?

Univariate Sensitivity Analysis:

The results are very robust. Changing any variable will always lead to a saving when using the Endo-SPONGE over the current process

Multivariate Sensitivity Analysis:

Even changing three variables at a time in an unfavorable way for Endo-SPONGE there is still an annual saving of more than £ 100.000 in Year 1.

What are the main sources of uncertainty about the model's conclusions?

The main sources of uncertainty are the three variables with the major impact on the final result:

- Patients OP Stage 1 Current Process
- Cost of re-operation
- Total cost to insert Endo-SPONGE per Session

There is still a saving if we change all variables +/- 25% (which is very unlikely to happen) in an unfavorable way for Endo-SPONGE.

The model results are very robust and they do not show significant uncertainties.

Miscellaneous results

Include any other relevant results here.

N/A

Validation

Describe the methods used to validate, cross-validate (for example with external evidence sources) and quality assure the model. Provide sources and cross-reference to evidence when appropriate.

N/A we have been unable to gain access to external clinical experts to validate the model

Give details of any clinical experts who were involved in validating the model, including names and contact details. Highlight any personal information as confidential.

N/A we have been unable to gain access to external clinical experts to validate the model

5 Summary and interpretation of economic evidence

Describe the main findings from the economic evidence and cost model. Explain any potential cost savings and the reasons for them.

Compared with current AL treatment pathway – introduction of Endo-SPONGE pathway would offer a cost savings of £261,995.90 within 1 year per 100 AL patients, with a saving of £725,026.12 in year 10 and an accumulative saving of £4,935,110.08 over 10 years per 100 AL patients.

Cost savings come from reducing number of secondary operations required to repair AL by 35.550 operations per 100 AL patients at a saving of £447,733.82 per year

Further cost savings come from reducing the number of patients with a permanent stoma by 16.519 patients per 100 AL patients saving £51,447.80 per year. As the number of permanent stoma patients will increase year on year, the annual saving on stoma cost will increase year on year. In year 10, the stoma cost saved in that year will be £514,478,03

Briefly discuss the relevance of the evidence base to the scope.

This economic model compare use of operative and non-operative treatments for resolution of AL with a move to more non-operative treatments initially (67.7%) with Endo-SPONGE pathway compared with current AL treatment pathways (42.8%) and with increase success rate of Endo-SPONGE an overall reduction of operations by 35.550 re-operations per year in the Endo-SPONGE pathway compared with current AL pathway...
The scope also included antibiotics use. The level of antibiotic use is not clear in the literature, being a potential initial treatment or used in conjunction with non-operative treatments and operative treatments. Antibiotics use in current AL pathway occurred at a rate of 51.5% and antibiotic use in Endo-Sponge was recorded at a high of 28.9% and reducing to 10.9% when clinicians made the decision to add antibiotics based on patient needs rather than study direction. While not included in the economic model, introduction of Endo-SPONGE pathway could allow for reduction of antibiotic use.

Briefly discuss if the results are consistent with the published literature. If they are not, explain why and justify why the results in the submission be favoured over those in the published literature.

Ashraf et al 2013, demonstrated cost of laparotomy at £20671 ± £11,301. This is lower than the cost of £12,594.36 used in the economic model here. Use of the costs according to Ashraft would demonstrate even greater savings with reducing the number of re-operations.

Ashraft et al 2013 estimate current conservative treatment costs for treating AL as £9686 ±2626 in the UK. This is lower than cost of £3,541.91 used in the analysis here.

Use of our cost analysis rather than published literature allowed for a consistent analysis and re-operation and non-operative costs were calculated by the same means in both pathways. Use of Ashraf et al data would have only provided cost for current non operative treatments and for Endo-SPONGE

Describe if the cost analysis is relevant to all patient groups and NHS settings in England that could potentially use the technology as identified in the scope.

The cost analysis is relevant to all patients and the decision trees covers all severities of AL

Briefly summarise the strengths and limitations of the cost analysis, and how these might affect the results.

Strengths: the analysis provides a simple cost comparison analysis reflecting clinical practice for AL treatment. The analysis utilises the best available data within the published literature. Sensitivity analysis of 10% variation demonstrated that model still holds up to scrutiny, and further sensitivity analysis of 25% variation demonstrated that the model is robust.

Weaknesses: The analysis has not been able to be verified by clinical experts due to time constraints. Lack of data directly comparing Endo-SPONGE with current non-operative treatments unavailable and due to the nature of the health issue, unlikely to be available. Lack of direct economic impact of Endo-SPONGE use in clinical setting.

Detail any further analyses that could be done to improve the reliability of the results.

Direct comparison (possible randomised control trial - RCT) of Endo-SPONGE compared with current non-operative treatment to monitor economic impact and patient outcomes – however due to low frequency of AL (up to 10% of all colorectal anastomoses) a RCT or any other direct comparison would be unlikely to be attainable.

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Please include all references below using NICE's standard referencing style.

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7 Appendices

Appendix A: Search strategy for Outcomes for Endo-SPONGE

Describe the process and methods used to identify and select the studies relevant to the technology being evaluated. See section 2 of the user guide for full details of how to complete this section.

Date search conducted:	5.9.19
Date span of search:	Conception to 5.9.19

List the complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean). List the databases that were searched.

Set#	Searched for TX	Results		
		CINAHL Complete, Medline Complete, Biomedical Reference Collection and STM	Cochrane Library	Pubmed
S1	Endo-SPONGE	162	1	25
S2	Endo-SPONGE	154	2	20
S3	Endoscopic vacuum therapy	3,829	8	337
S4	Endoscopic vacuum-assisted	1,181	10	89
S5	Transanal vacuum therapy	278	1	10
S6	ETVARD	18	0	2
S7	S1 OR S2 OR S4 OR S4 OR S5 OR S6 6	4,159	13	381
S8	Rectum	296,886	-	73,827
S9	Colorectal	750,866	-	165,477
S10	Rectal	428,841	-	114,688
S11	anorectal	40,733	-	11,163
S12	S8 OR S9 OR S10 OR S11	1,152,925	-	287,097
S13	Anastomotic leak	31,530	-	6261
S14	S7 And S12 AND S13	605	13	32
S14	S14 NOT eosophagus	257		

Total = 302

Brief details of any additional searches, such as searches of company or professional organisation databases (include a description of each database):

Previous company search Date: 24th December 2018 and 2nd January 2019
EMBASE and Google Scholar Endo-SPONGE or Endo-SPONGE
Limitations:

- Time period: 2012 – January 2019
- English and Spanish language

Papers not already included in initial search n= 13. These papers were included at stage for full paper analysis

Inclusion and exclusion criteria:

Inclusion criteria	
Population	Lower gastrointestinal tract anastomotic leaks.
Interventions	Endo-SPONGE alone.
Outcomes	Success of stopping leak and time taken. Closure of protective stoma and time taken. Complication rate.
Study design	Systematic reviews, randomised, non-randomised, cohort, observational Case series, Case studies and qualitative studies.
Language restrictions	No language restrictions.
Search dates	5.9.19
Exclusion criteria	
Population	Upper gastrointestinal tract anastomotic leaks
Interventions	Endo-SPONGE in conjunction with other interventions (early surgical closure, over scope clips etc.). Any non Endo-SPONGE endoscopic vacuum therapy. Any other intervention other than endoscopic vacuum therapy. Used outside of device instructions for use (e.g. colonoscopy perforation).
Outcomes	
Study design	Testimonials, non-systematic reviews containing no primary data, editorials, reports describing product news. In vitro studies.
Language restrictions	Unable to obtain translation.
Search dates	5.9.19

Data abstraction strategy:

Data extracted:

- Number of participants.
- Protective stoma/ stoma after AL detection
- Early/ late anastomosis detection/treatment initiation
- Frequency of Endo-SPONGE change.
- Number of Endo-SPONGE sessions.
- Time to healing/duration of therapy.
- Success of treatment.
- Stoma reversal rate.
- Time to stoma reversal.
- Complication rate.
- Sepsis after treatment
- Costs and costs notes
- Rate of bowel continuity.
- Antibiotic use as well

- Abscess size.
- 30 day Mortality rate/long term mortality.
- Length of stay.
- In/Out patient treatment.
- Long term success rate.
- Need for extra surgery.
- Additional endoscopy procedures
- Quality of life
- Comments

Data Abstraction

Study	N	Protective stoma n (%) stoma after AL	Earl / late anastomosis, treatment initiation	Frequency of changing sponge	Median number of sessions (range) mean ± SD	Median duration of therapy in days/ (range) mean ± SD	Success of treatment (%)	Stoma reversal	Time to stoma reversal	Complications (%)	Sepsis after treatment n (%)	Costs and cost notes
Arezzo et al, (Arezzo et al. 2015a) 2015	14	8/14 (57) yes 6/14 (43) no N= 3 diverted after AL identified	10/14 (71) acute (early) <60 days 4/14 (29%) chronic (late) > 60 days Diagnosis	2-3 times per week	12.5 (4-40)	40.5 (8-114)	11/14 (78.5) overall 9/10 (90%) acute (early)leaks 2/4 (50%) chronic (late) leak (p=0.18) 8/8 (100%) with stoma initially 3/6 (50%) No stoma initially (p=0.055) 8/10 (80%) 25% leak 1/1 (100%) 50% leak 2/3 (66%) 75% leak	N/A	N/A	0/14 (0)	1/14 (7) overall developed sepsis 1/10 (10) acute 0/4 (0) Chronic	180 Euro/device 70 Euro (15 min endoscopy 1 Dr 1 nurse) median cost 3125 (1,000-10,000)
Boschetti et al 2018	29	21/29 (72) yes 8/29 (28) no N=0 diverted after AL identified	12/29 (41) early < 30 days 17/29 (59) >30 days Diagnosis	Every 3-5 days	18.6 (4-57)	70 (14-196) overall 70 (14-196) with stoma 56 (14-98) No stoma	27/29 (93) overall 19/21 (90) With stoma 8/8 (100) No stoma No correlation to time of AL discovery and closure (Rho=0.45 p=0.12)	18/21 (87.5)	After 6 months 18 patients (85.7%) had reversal	0/29 (0)	N/A	Treatment without sedation as out patient
Huisman et al 2019	20	14/20 (70) yes 6/20 (30) no N=4 diverted after AL detected	10/20 (50) early 10/20 (50) late Treatment NOT diagnosis	Change 2x per week	9 (2-28)	25 (3-115) All 20 (3-115) early 25 (5-80) late p=0.79	17/20 (80%) all 8/10 (80) early 9/10 (90) late	14/18 (77.8%)	10 mo(3-15) all 7 (3-11) early 10 (6-15) late p=0.15	chronic sinus 3/20 (15) all 2/10 (20) early 1/10 (10) late	N/A	N/A
Jimenez-Rodriguez et al 2018	22	13/13 (100) yes following LAR N= 0 diverted after AL identified	15/22 (68) early treatment < 6 weeks 7/22 (32) late treatment > 6 weeks	Every 3-5 days	3.1 ±1.9	22.3 ±14.7	19/22 (86) Onset of therapy <6weeks p=0.041 (no data) Cavity size p=0.226	5/13 (38.5%) ileostomy	N/A	0/22 during treatment 3/22 after treatment (13.6) n=1 stenosis, n=1 chronic fistula, n= 1 osetomylitis	N/A	Cost for ambulatory stay/day US$80
Katz et al 2018	6	3/6 (50) yes 3/6 (50) no N= 2 diverted after AL identified	6/6 (100) early < 14 days, treat < 17 days	N/A	N/A	N/A	6/6 (100)	4/5 (80) 1/5 new tumour prevented closure	N/A	N/A	6/6 sepsis was controlled	N/A
Keskin et al, 2015	15	N/A	8/15 (53) early <30 days	Every 3-4 days	2.2 (1-5)	NA	12/15 (80) all 6/8 (75%) early 6/7 (85%) late	10/14 (71) n=3 died due to disease	N/A	3/15 (20) n=2 sepsis n=1 bleeding	N/A	N/A

Study	N	Protective stoma n (%) stoma after AL	Earl / late anastomosis, treatment initiation	Frequency of changing sponge	Median number of sessions (range) mean ± SD	Median duration of therapy in days/ (range) mean ± SD	Success of treatment (%)	Stoma reversal	Time to stoma reversal	Complications (%)	Sepsis after treatment n (%)	Costs and cost notes
			average 15 (6-27d) 7/15 (47) late 173 (43-343d)					progression before closure				
Kuehn et al, 2016	20 AL 41 total	19/20 (95) yes AL	N/A	Every 3 days	7(1-37) AL 6 (1-37) total	23 (2-109) AL 20 (2-131) total	18/20 (90) AL 34/41 (83) total	15/19 (79) AL	244 days (152-488 days)	4//20 (15) N=1 bleeding N=3 stenosis	27/32 sepsis controlled	N/A
Manta et al 2016	7	N/A	1/7 (14) early 6/7 (86) late	N/A	N/A	N/A	7/7 (100)	N/A	N/A	N/A	N/A	N/A
Milito et al 2017	14	14/14 (100) yes protective stoma	14 (7-21)days AL detected		3-14	35(16-51) treatment 37 (19-55) healing time	N/A	N/A	N/A	0/14	N/A	N/A
Mussettos et al 2017	11	N/A	N/A	Every 2-3 days	16 (9-23)	37 (18-65)	10/11 (91)	N/A	N/A	2/11 (18) anastomotic stricture	N/A	N/A
Nerup et al, 2013	13	N/A	N/A	Every 2-3 days	N/A	18 (3-40)	13/13 (100)	12/13 (92%)	N/A	1/13 (7.6) stenosis	N/A	N/A
Riss et al, 2009	6 AL 9 total	1/6 (11) yes protective stoma AL N=3 diverted after AL identified 2/6 (22) no stoma AL 3/3 (100) Hartmann = stoma	1/9 (11) early = 7 days 8/9 (89) late = 2.5 (1-24mo) for total 8 weeks to LAR AL 10 weeks to Hartmann's leak	Every 2-3	N/A	21 (14-56) total	6/9 (67) total 5/6 (83) AL 1/3 (33) Hartmann's	N/A	N/A	0/6 (0)	N/A	Duration of Endo-SPONGE insertion 15 min (5-65)
Riss et al, 2010	23	14/23 (61) yes N=2 diverted after AL identified	N/A	Every 2-3 days	N/A	21 (range 7-106)	20/23 (87) initial	13/17 (76.5)	N/A	6/23 (30) long term complications N=1 stenosis N=5 recurrent abscess	N/A	N/A
Rottoli et al 2018	8	N/A	N/A	Every 2-3 days	3 (1-10)	12 (3-32)	8/8 (100)	7/8 (87.5) 1 pt chose to delay closure	2.5 (1-6) months after closure	N/A	N/A	N/A
Srinivasamurthy et al, (Srinivasa	8		29 (10-115) days to AL detection	NA	4 (1-7)	26 (7-49)	6/8 (75) all	5/8 (62.5)		2/8(25) N=1 fistula		N/A

Study	N	Protective stoma n (%) stoma after AL	Earl / late anastomosis, treatment initiation	Frequency of changing sponge	Median number of sessions (range) mean ± SD	Median duration of therapy in days/ (range) mean ± SD	Success of treatment (%)	Stoma reversal	Time to stoma reversal	Complications (%)	Sepsis after treatment n (%)	Costs and cost notes
murthy et al. 2013a) 2013		N/A	5/8 (62.5) < 6 weeks 3/8 (37.5) >6 weeks from surgery to sponge placement						41 months (10-45 months)	n=1 inadvertent placement of Endo-SPONGE	N/A	
Strangio et al, 2015	25	13/25 (52) yes preventative	17 (15-100) days to AL detection 16 (0-53) days from detection to Endo-SPONGE insertion	Every 2-3 days	9 (1-39)	28 (7-128)	22/25 (88)	11/13(84.)	N/A	3/25 (12) N=1 urethirc fistula, n=1 ileal fistula N=1 pararectal abscess	N/A	N/A
van Koperen et al, 2009	16	8/16 (50) yes preventative N=7 diverted after AL identified	11 (3-150) days after AL discovery 8/16 (50) early < 6 weeks 24 (13-39) days 8/16 (50) late > 6 weeks 74 (43-1,602) days	Every 3-4 days	13 (8-17)	40 (28-90)	9/16 (56.2)	5/9 (56%)	N/A	4/16 (25) N=1 bleeding 500 cc N=1 pain stopped therapy N=1 stopped due to near complete dehiscent anastomosis N=1 recurrent abscess.	0/16 developed peritonitis	N/A
Weidenhagen et al, 2008	34 all 29 PP	21/29 yes protective stoma N=3 stoma created after AL detection N=1 stoma created after Endo-SPONGE treatment	8.2±3.6 days after surgery AL discovered	Every 2-3 days	11.4 ±6.3 (range 1-27)	34.4 (4-79)	28/34 (82.3)	22/25 (88)	168.9±81.7 days	3/34 N=2 ischemic necrosis N=1 rectovaginal fistula	N/A	N/A
Total	315	N/A	N/A	N/A	N/A	N/A	238/277 (85.9%)	141/183 (77.0%)	N/A	34/270 (12.6)	N=1 sepsis developed /54	N/A
weighted mean 95% CI	N/A	N/A	N/A	N/A	10.7 (8.0-13.5)	38.1 (30.1-46.1)	88.8 (85.2-92.4)	79.0 (71.9-86.1)	10.41 month (7.05-13.77)	10.0 (5.7-14.2)	N/A	N/A

Study	N	bowel continuity	Antibiotics as well	Abscess size cm (mean, median)	Distance from anal verge	Mortality 30d/ long term	LOS days	In/out pt	Long term success	Need for extra surgery	Additional endoscopic treatment	Quality of life
Arezzo et al, (Arezzo et al. 2015a) 2015	14	N/A	N/A	5.0 4cm (2-9)	N/A	0/14	7 days for 10/14	4/14 all OP 14/14 OP after 7 days	N/A	3/14 (21.4%) diverting stoma created	2/14 (14.3%) OTSC 1/14 (7.1%) Glue	N/A
Boschetti et al 2018	29	N/A	12/29 (41%) b4 endo – stopped by d 10	7.0 7±4.6cm (2-20cm)	6.2±4.6cm (2-20cm)	0/29	N/A	29/29 out patients	24/29 (83%)	1/29 definitive end stoma	N/A	N/A
Huisman et al 2019	20	14/20 (70) all 7/10(70) early 7/10(70) late	n=1 before endo treatment	N/A	8.5cm (5-12cm)	0/20	N/A	N/A	N/A	6/20 (30%) definitive stoma n=3, n=1 proctectomy, n=1 recurrence n=1 tumour progression	N/A	Increased LARS (endo sponge + AL) 37 (23-42) versus no AL 30 (4-41) P=0.009
Jimenez-Rodriguez et al 2018	22	5/13 (38.5)	1/22 (4.5%)	5.9±1.9cm ALL 5.3±1.8cm LAR 6.6 ±2.1cm Hartmann	4.92±1.9cm	0/22 3/22(13) died long term follow up	N/A	11/22 outpatients	15/22 (68.2%) 4/22 (18.2%) second course of endo n= 3 success 18/22 (81.8%)	2/22 (9.1%)	10/22 (45%) glue after cavity too small for Endo-SPONGE	N/A
Katz et al 2018	6	5/6 (83)	1/6 (16.7%) with endo	N/A	N/A	0/6	N/A	N/A	N/A	2/6 (33.3%) diverting stoma	N/A	N/A
Keskin et al, 2015	15	12/15 (80)	N/A	N/A	N/A	0/15 (0) 30 day follow op 3/15 (20)long term follow up	N/A	3/15 out patient	N/A	3/15 (20%)	N/A	N/A
Kuehn et al, 2016	20 AL	N/A	N/A	N/A	N/A	0/20	N/A	N/A	N/A	N/A	N/A	N/A
Manta et al 2016	7	N/A	N/A	3 median 2.9 mean (1.5-5cm)	N/A	0/7	0 treated as O/P	7/7 outpatient	N/A	0/7	0/7	N/A
Milito et al 2017	14	N/A	14/14	Median 8.1 x4.6cm	N/A	N/A	N/|A	14/14 out patient	N/A	N/A	N/A	N/A
Mussettos et al 2017	11	N/A	N/A	7.5cm (4-12cm)	4.5cm (2-8cm)	0/11 30 d 2/11 (18) long term	N/A	N/A	10/10 (100%)	1/11 (9%) re-op converted to Hartmann's	1/11 dilation 8mo after healing, 1/11 stent 5 mo stent fitted	N/A
Nerup et al, 2013	13	N/A	N/A	N/A	N/A	0/13	25 days (7-39)	N/A	N/A	1/13 reoperated permanent stoma	2/13 moved to conservative treatment	N/A
Riss et al, 2009	9					1/9 heart attack		N/A		3/9 (33)total		Satisfaction 3 (0-9)

Study	N	bowel continuity	Antibiotics as well	Abscess size cm (mean, median)	Distance from anal verge	Mortality 30d/ long term	LOS days	In/out pt	Long term success	Need for extra surgery	Additional endoscopic treatment	Quality of life
		N/A	N/A	N/A	N/A		N/A		N/A	N=resection after Hartmann's N=Hartmann's after AL	N/A	Altered daily life 5 (1-9) Pain 3 (0-6) Would you repeat treatment 6/9 = yes, 2/9 = no
Riss et al, 2010	23 all 20 PP	N/A	N/A	N/A	N/A	0/23 30 day 4/23 (17) long term follow up	N/A	N/A	15/20 (75%) all	3/20 anastomosis taken down and Hartmann's 1/20 CT guided drainage	1/20 (5%) glue 1/20 (5%) anal stent	
Rottoli et al 2018	8	N/A	N/A	N/A	N/A	0/8	15.5 (6-48) median	0/8 outpatient	8/8	1/8 n=1 loop ileostomy before Endo-SPONGE treatment	N/A	0/8 reported incontinence to faeces or gas. Daytime bowel movement 5 (3-8) night time bowel movement 1.7 (1-4)
Srinivasamurthy et al, (Srinivasamurthy et al. 2013a) 2013	8	5/8(62.5) all 4/5 (80) early 1/3 (33) late,	N/A	N/A	N/A	0/8	N/A	N/A	N/A	2/8 (37.5%) N=1 abdominoperineal excision of rectum, n=1 Hartmann's	N/A	N/A
Strangio et al, 2015	25	11/13 (84)	N/A 2/25 (8%)antibiotics (failed pt)	5.6 (1.5-10.0cm) median	N/A	0/25 30 day 3/25 (12) n=2 cancer n=2 vascular accident	N/A	N/A	N/A	2/25 (8%) re-operation	1/25 (4%) CT guided drainage	N/A
van Koperen et al, 2009	16	N/A	N/A	N/A	5cm (2-8cm)	0/16	N/A	N/A	N/A	2/16 inter sphincteric proctectomy	N/A	N/A
Weidenhagen et al, 2008	34 all 29 PP	N/A	N/A	2 – 20 (7.4±5.1cm)	5.3cm (1-12cm)	1/34 fell out of bed	Mean 30.5±12.8 (10-69)	25/29 outpatient	N/A	5/34 within 1 week/ 1-2 sessions N=1 after Endo-SPONGE treatment N=1 Hartmann's	N/A	N/A
Total	292	47/67 (70.1)	31/116 (26.67) overall 18/67 (26.86) WITH Endo-SPONGE	N/A	N/A	5/262 (1.9) 30d 17/262 (6.5) long term		103/130 (79)	72/89 (80.9)	37/257 (14%)	25/126 (20)	N/A

Study	N	bowel continuity	Antibiotics as well	Abscess size cm (mean, median)	Distance from anal verge	Mortality 30d/ long term	LOS days	In/out pt	Long term success	Need for extra surgery	Additional endoscopic treatment	Quality of life
			13/49 (25.5) Before Endo-SPONGE									
Meta-analysis weighted mean (95% CI_	N/A	72.1 (56.9-87.3)	28.9 (-6.45-64.2	5.82cm (4.58-7.10cm)		2.8 (0.9-4.8) 30d 4.3 (1.9-6.6) long term	25.3 days (19.6-31.1) Outpatient not included	79.8 (65.7-94)	84.8% (95% CI 74.8 to 94.7)	11.0% (7.0-15.0)		N/A

Excluded studies

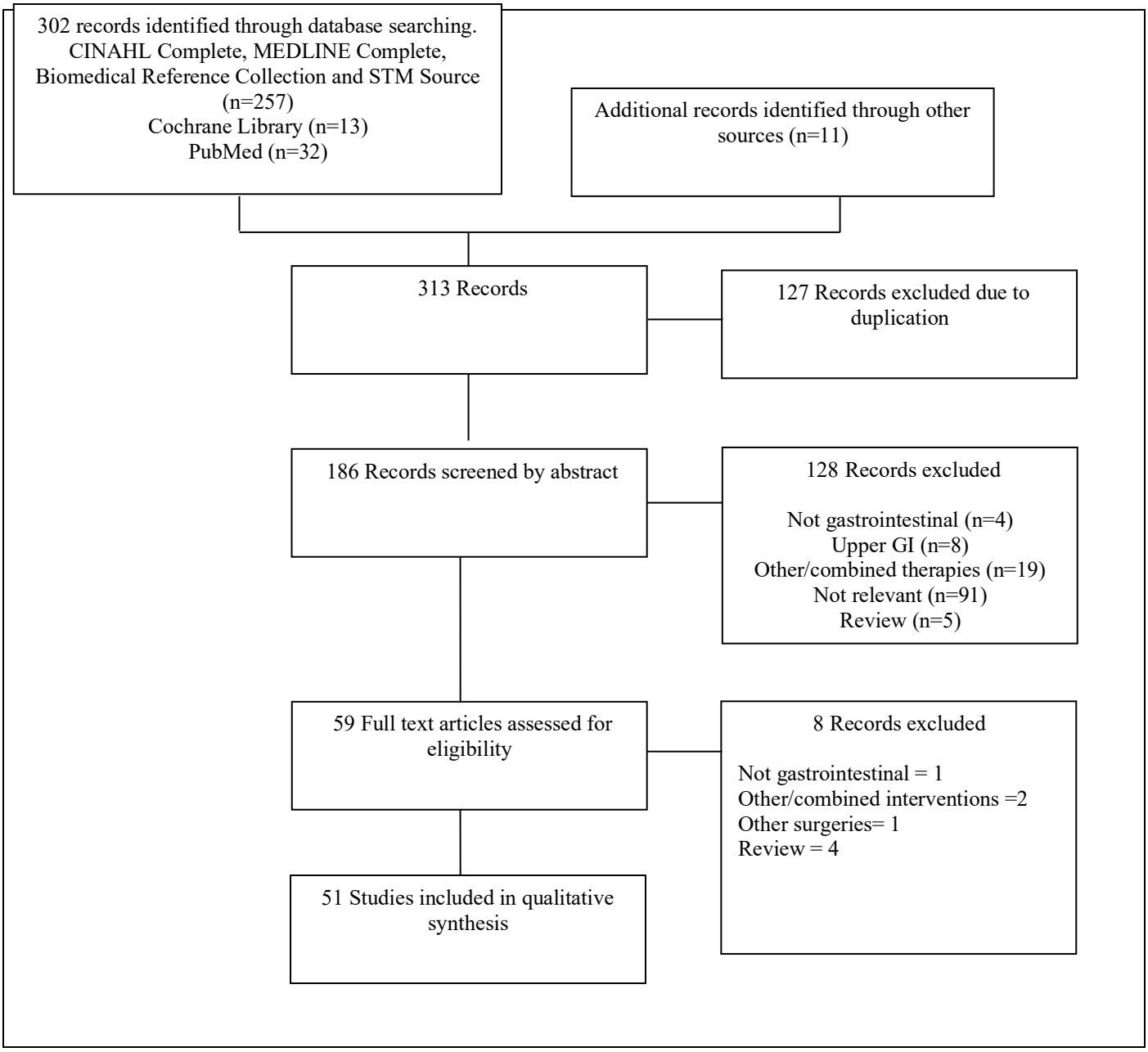
List any excluded studies below. These are studies that were initially considered for inclusion at the level of full text review, but were later excluded for specific reasons.

Author	Title	Exclusion reason	Company comments
(Arezzo et al. 2010)	Endoluminal vacuum therapy for anastomotic leaks after rectal surgery	Case studies n=3	Descriptive data only
(Bemelman 2009)	Vacuum assisted closure in coloproctology	Review	No primary data
(Borejsza-Wysocki et al. 2015)	Endoscopic vacuum-assisted closure system (E-VAC): case report and review of the literature	Use of non Endo-SPONGE device, case study, review	Device used is not CE marked and indicated for use for endoscopic vacuum therapy
(Borstlap et al. 2018)	Vacuum-assisted early transanal closure of leaking low colorectal anastomoses: the CLEAN study	Endo-SPONGE in conjunction with surgical closure	Other therapy – cannot be assured effect from Endo-SPONGE
(Chopra, Mrak, and Hunerbein 2009)	The effect of endoscopic treatment on healing of anastomotic leaks after anterior resection of rectal cancer	No primary data for Endo-SPONGE	No primary data
(Cirocchi et al. 2013)	Treatment of Hinchey stage III-IV diverticulitis: a systematic review and meta-analysis.	Not Anastomotic leak	
(D'Hondt et al. 2009)	Chronic pelvic abscedation after completion proctectomy in an irradiated pelvis: another indication for Endo-SPONGE treatment?	Case studies n=1	Descriptive data only
(Durai and Ng 2010)	Surgical Vacuum Drains: Types, Uses, and Complications	Review, non Endo-SPONGE irrelevant	Device used is not CE marked and indicated for use for endoscopic vacuum therapy
(Einenkel, Holler, and Hoffmeister 2011)	Sonographic diagnosis and Endo-SPONGE assisted vacuum therapy of anastomotic leakage following posterior pelvic exenteration for ovarian cancer without using a protective stoma	Case study n=1	Descriptive data only
(Eriksen, Ovesen, and Gögenur 2018)	Short- and long-term outcomes after colorectal anastomotic leakage is affected by surgical approach at reoperation	No primary data on Endo-SPONGE	

Author	Title	Exclusion reason	Company comments
(Gardenbroek et al. 2015)	Early reconstruction of the leaking ileal pouch-anal anastomosis: a novel solution to an old problem	Endo-SPONGE in conjunction with surgical closure	Other therapy – cannot be assured effect from Endo-SPONGE
(Glitsch 2008)	Endoscopic transanal vacuum-assisted rectal drainage (ETVARD): an optimized therapy for major leaks from extra peritoneal rectal anastomoses	Use of non Endo-SPONGE device	Device used is not CE marked and indicated for use for endoscopic vacuum therapy
(Heeney, Mulsow, and O'Connell 2010)	Vacuum-assisted closure of chronic anorectal fistula	Case studies n=2	Descriptive data only
(Hoogenboom, Hoff, and Koopal 2010)	Small intestinal-colorectal anastomotic fistula developing during Endo-SPONGE treatment	Case study n=1	Descriptive data only
(Knuth et al. 2013)	Transrectal ultrasound-guided endoscopic drainage and vacuum therapy of pelvic abscesses: an alternative to (computed tomography-guided) percutaneous drainage	Case study n=1	Descriptive data only
(Mencio et al. 2018)	Use of a novel technique to manage gastrointestinal leaks with endoluminal negative pressure: a single institution experience	Use of non Endo-SPONGE device	Device used is not CE marked and indicated for use for endoscopic vacuum therapy
(Mario Martinotti 2014)	Combined endoscopic transanal vacuum assisted rectal drainage: A novel therapy for colorectal anastomotic leak after TME for Cancer	Case studies n=4	Descriptive data only
(Nagell and Holte 2006)	Treatment of anastomotic leakage after rectal resection with trans rectal vacuum-assisted drainage (VAC). A method for rapid control of pelvic sepsis and healing	Use of non Endo-SPONGE device	Device used is not CE marked and indicated for use for endoscopic vacuum therapy
(Okoshi et al. 2013)	Efficacy of transanal drainage for anastomotic leakage after laparoscopic low anterior resection of the rectum	Not vacuum assisted treatment	
(Perathoner et al. 2010)	Damage control with abdominal vacuum therapy (VAC) to manage perforated diverticulitis with advanced generalized peritonitis--a proof of concept	Not anastomotic leak, not Endo-SPONGE	
(Richterich et al. 2008)	Endo-SPONGE a new endoscopic treatment option in colonoscopy	Use outside of IFU for Endo-SPONGE Case study n=1	

Author	Title	Exclusion reason	Company comments
(Runkel N. 2014)	Endoluminal Negative Pressure Wound Therapy (E-NPWT) for anastomotic leakage after rectal resection	Use of non Endo-SPONGE device	Device used is not CE marked and indicated for use for endoscopic vacuum therapy
(Shelygin et al. 2018)	Meta-analysis of management of colorectal anastomotic leakage	Unable to translate	
(Sumrien et al. 2016)	The use of a negative pressure wound management system in perineal wound closure after extralevator abdominoperineal resection for rectal cancer (ELAPE) for low rectal cancer	Poster abstract	
(Terzian et al. 2016)	Repair of Coloanal Anastomotic Dehiscence and Sinus Formation Using Intraluminal Application of Endo-SPONGE®	Case study n=1, non anastomotic leak	Descriptive data only
(Van Koperen et al. 2008)	Endo-SPONGE treatment of anastomotic leakage after ileo-anal pouch anastomosis: report of two cases	Case studies	Descriptive data only
(Verlaan et al. 2011)	Early, minimally invasive closure of anastomotic leaks: a new concept	Endo-SPONGE in conjunction with surgical closure	Other therapy – cannot be assured effect from Endo-SPONGE
(von Bernstorff et al. 2009)	ETVARD (endoscopic transanal vacuum-assisted rectal drainage) leads to complete but delayed closure of extra peritoneal rectal anastomotic leakage cavities following neoadjuvant radiochemotherapy	Use of non Endo-SPONGE device	Device used is not CE marked and indicated for use for endoscopic vacuum therapy
(Wood, Wright, and Witherspoon 2015)	Fungal endophthalmitis: an unusual complication of GI surgery and endoluminal vacuum therapy	Case study n=1	Descriptive data only
(Worley et al. 2018)	Management of early pouch-related septic complications in ulcerative colitis: a systematic review	Not Anastomotic leak	

Report the numbers of published studies included and excluded at each stage in an appropriate format (e.g. PRISMA flow diagram).



Structured abstracts for unpublished studies

Study title and authors
Introduction
Objectives
Methods
Results
Conclusion
Article status and expected publication: Provide details of journal and anticipated publication date

No Unpublished studies

Appendix B: Search strategy for Current anastomotic leak outcome

Date search conducted:	15.10.19
Date span of search:	Conception until 15.10.19

List the complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean). List the databases that were searched.

Enter text.

Set#	Searched	Results		
		CINAHL Complete, Medline Complete, Biomedical Reference Collection and STM	**Cochrane Library**	**Pubmed**
S1	Anastomotic leak (TI)	1,346	1	401
S2	Anorectal (TX)	41,102	65	10,767
S3	Colorectal (TX)	760,006	348	152,107
S4	Rectal (TX)	432,350	445	112.285
S5	Rectum (TX)	299,056	233	64,992
S6	S2 OR S3 OR S4 OR S5	1,164,841	739	273,656
S7	Outcome* (TX)	8,282,063	7796	2,312,673
S8	S1 AND S6 AND S7	356	1	80
	total	437		

Brief details of any additional searches, such as searches of company or professional organisation databases (include a description of each database):

Inclusion and exclusion criteria:

Inclusion criteria	
Population	Lower gastrointestinal tract anastomotic leaks
Interventions	Standard intervention to resolve anastomotic leak (re-operation, non-operative conservative interventions, antibiotics and percutaneous drain)
Outcomes	Success of stopping leak and time taken Closure of protective stoma and time taken 30 day mortality rate Complication rate Length of stay
Study design	Systematic reviews, randomised, non-randomised, cohort, observational Case series, Case studies and qualitative studies.
Language restrictions	No Language restrictions
Search dates	15.10.19
Exclusion criteria	
Population	Upper gastrointestinal tract or bariatric anastomotic leaks, Non gastrointestinal.
Interventions	Interventions to prevent AL Any new test/non-standard treatment of AL Anastomotic sinus
Outcomes	
Study design	Testimonials, comments, non-systematic reviews containing no primary data, editorials, reports describing product news. In vitro or animal studies.
Language restrictions	Unable to obtain translation
Search dates	15.10.19

Data abstraction strategy:

Data Abstracted:

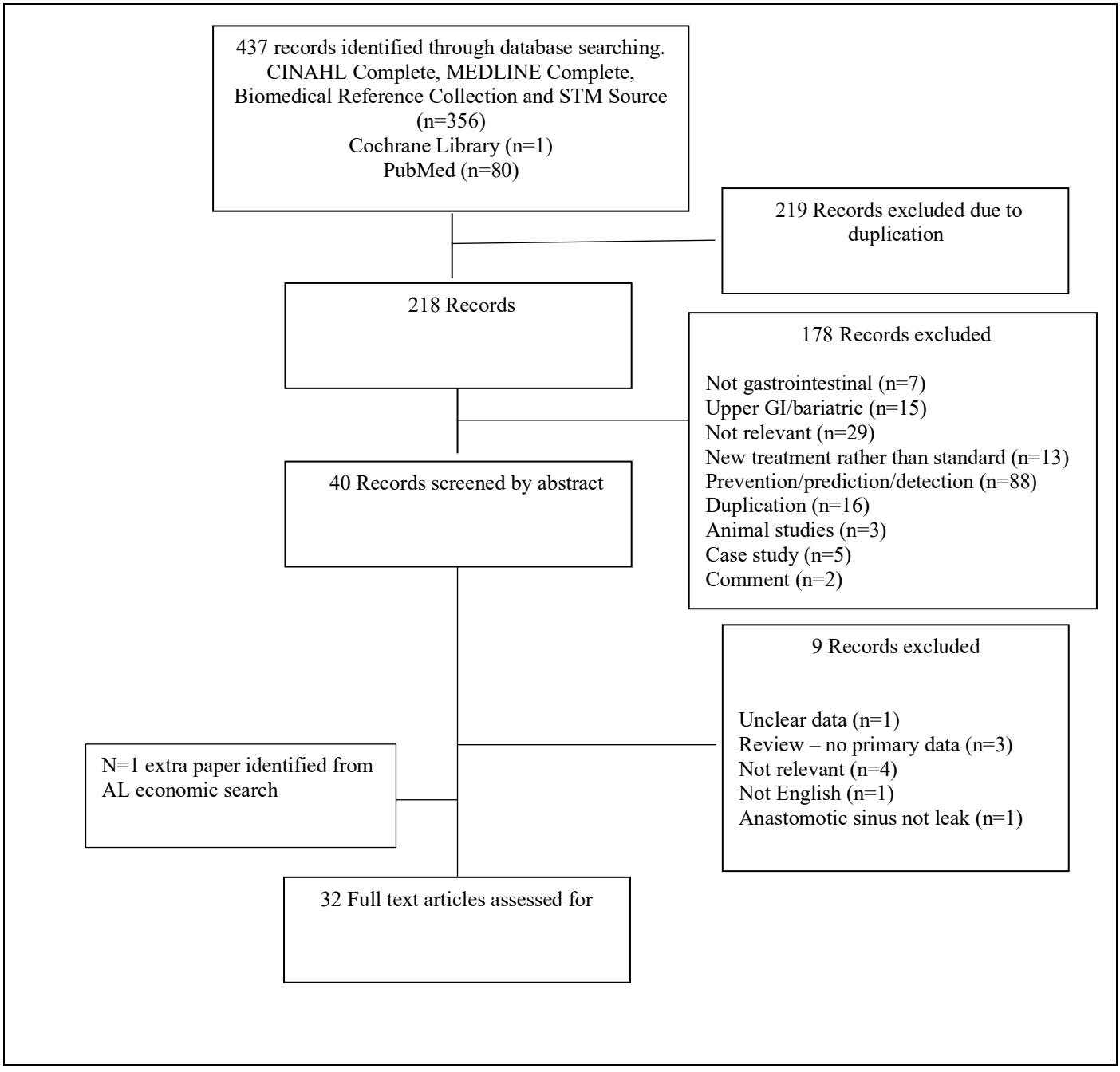
- Incidence of AL
- Intervention used (operative or non-operative)
- Type and rate of non-operative intervention (percutaneous drain, antibiotics)
- Success rate of intervention and overall
- Stoma reversal rate
- Length of stay
- 30 day mortality rate

Excluded studies

List any excluded studies below. These are studies that were initially considered for inclusion at the level of full text review, but were later excluded for specific reasons.

Author	Title	Exclusion reason	Company comments
(Phan et al. 2019)	Does a stoma reduce the risk of anastomotic leak and need for re-operation following low anterior resection for rectal cancer: systematic review and meta-analysis of randomized controlled trials.	Not relevant – looking at AL prevention	
(Phitayakorn et al. 2008)	Standardized algorithms for management of anastomotic leaks and related abdominal and pelvic abscesses after colorectal surgery	Systematic review, no treatment or outcome frequency	

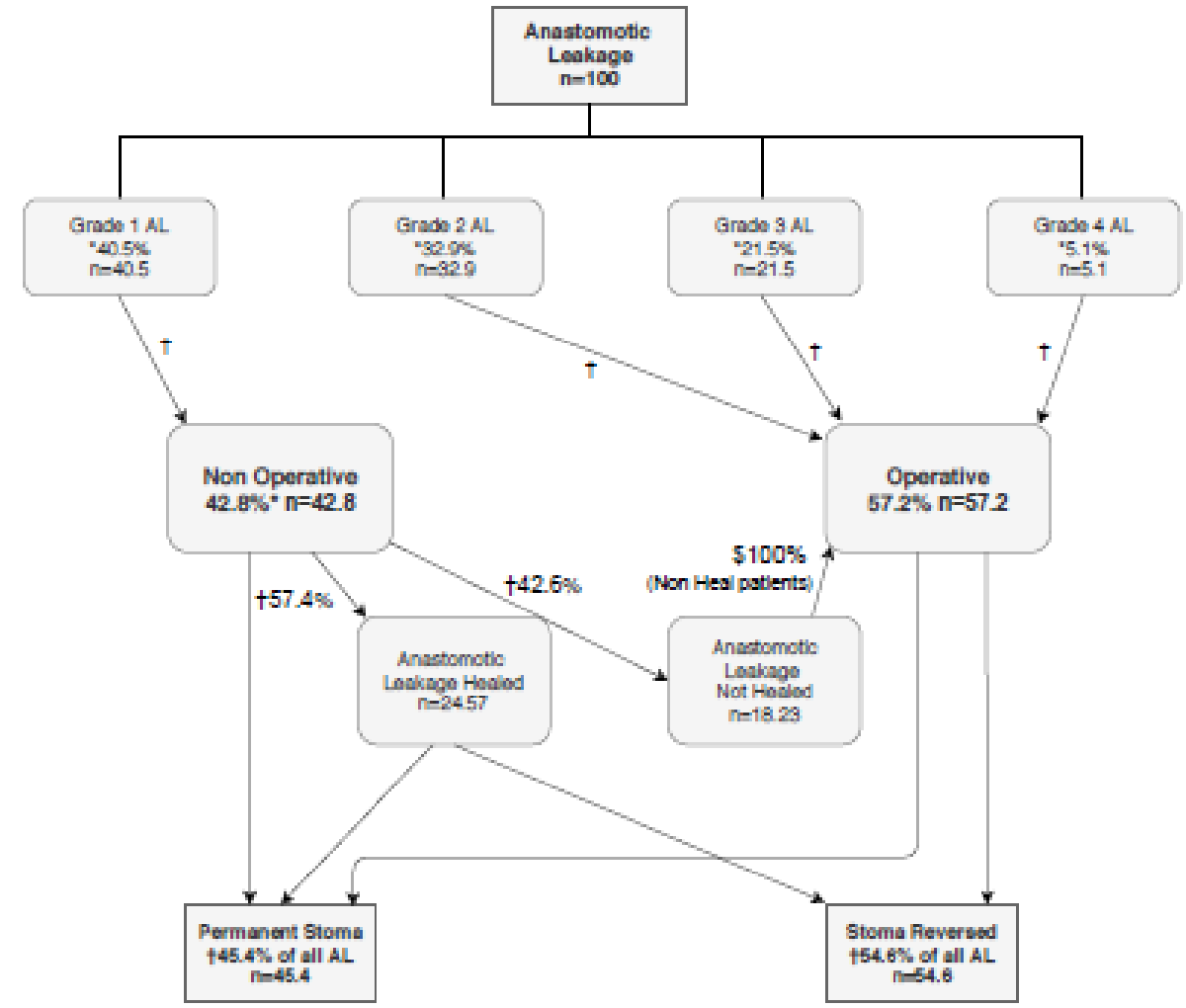
Report the numbers of published studies included and excluded at each stage in an appropriate format (e.g. PRISMA flow diagram).



Appendix C: Model structure

Please provide a diagram of the structure of your economic model.

Current Process

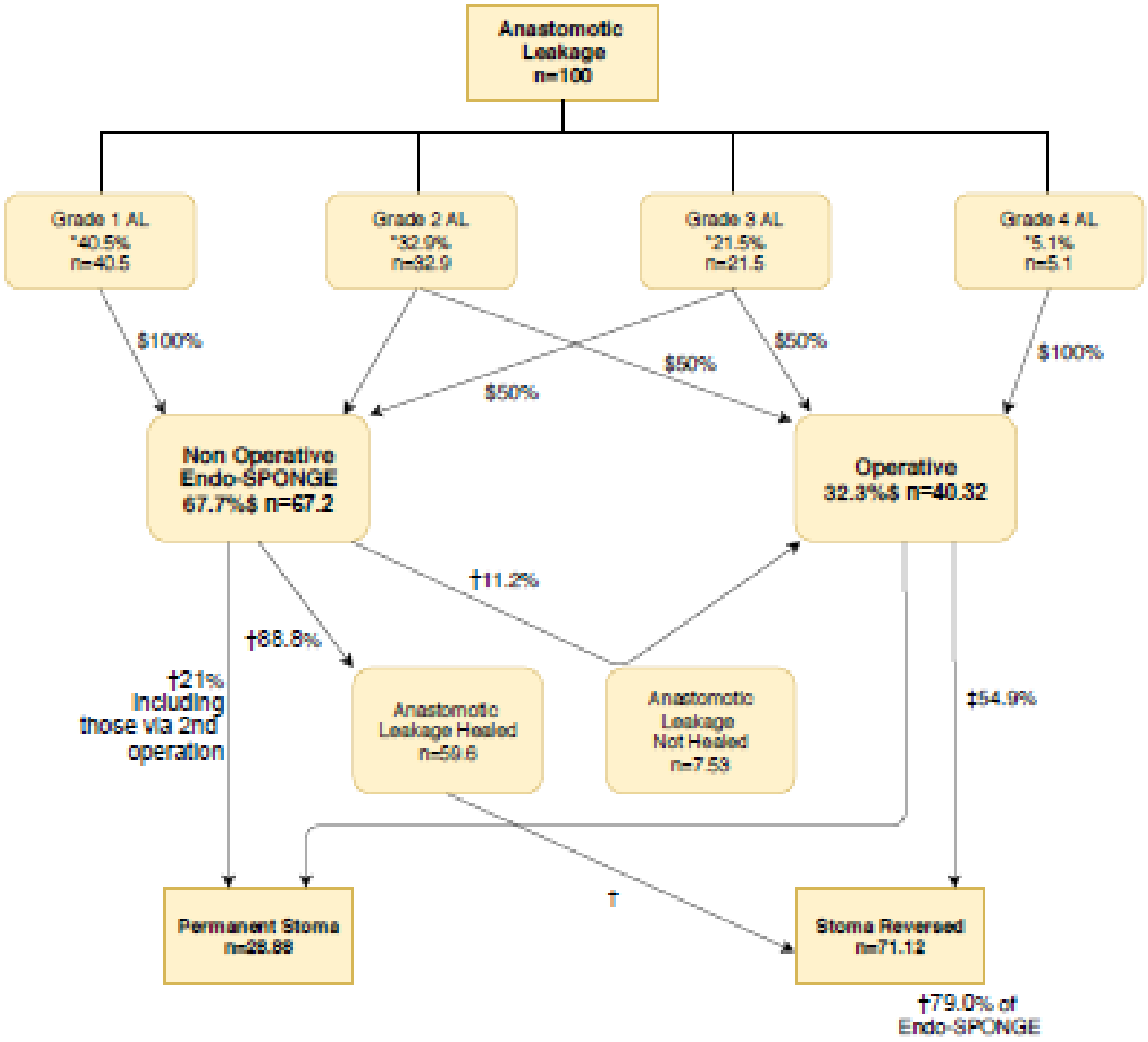


* = Asteria et al.

$ = Assumption.

† = Meta-analysis. Note: Stoma reversal figure of 52.7% on ALL current AL patients, irrespective of treatment.

Endo-SPONGE Process



* = Asteria et al.

$ = Assumption.

† = Meta-analysis.

‡ = Current AL data.

Appendix D: Search strategy for Current anastomotic leak Economics

Date search conducted:	23.01.2020
Date span of search:	Conception until 15.10.19

List the complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean). List the databases that were searched.

Set#	Searched	Results		
		CINAHL Complete, Medline Complete, Biomedical Reference Collection and STM	**Cochrane Library**	**Pubmed**
S1	Anastomotic leak	12,393	58	6940
S2	economic	2,060,119	2707	915006
S3	Anorectal (TX)	41,604	65	10892
S4	Colorectal (TX)	783,368	356	155533
S5	Rectal (TX)	439,403	450	113533
S6	Rectum (TX)	303,289	233	655613
S7	S3 OR S4 OR S5 OR S6	1,193,703	750	278,366
S8	S1 AND S2 AND S7	100	14	45

Brief details of any additional searches, such as searches of company or professional organisation databases (include a description of each database):

Inclusion and exclusion criteria:

Inclusion criteria	
Population	Lower gastrointestinal tract anastomotic leaks
Interventions	Standard intervention to resolve anastomotic leak (re-operation, non-operative conservative interventions, antibiotics and percutaneous drain)
Outcomes	Economic analysis in GB£
Study design	Systematic reviews, randomised, non-randomised, cohort, observational Case series, Case studies and qualitative studies.
Language restrictions	No Language restrictions
Search dates	23.01.2020
Exclusion criteria	
Population	Upper gastrointestinal tract or bariatric anastomotic leaks, Non gastrointestinal.
Interventions	Interventions to prevent AL Any new test/non-standard treatment of AL Anastomotic sinus
Outcomes	Economic values not in GB£
Study design	Testimonials, comments, non-systematic reviews containing no primary data, editorials, reports describing product news. In vitro or animal studies.
Language restrictions	Unable to obtain translation
Search dates	23.01.2020

Data abstraction strategy:

Data Abstracted:

- Economic impact without AL
- Econoic impact with AL
- Economic impact of stoma following colorectal surgery
- Any economic impact following AL
- Any economic impact without AL for comparison

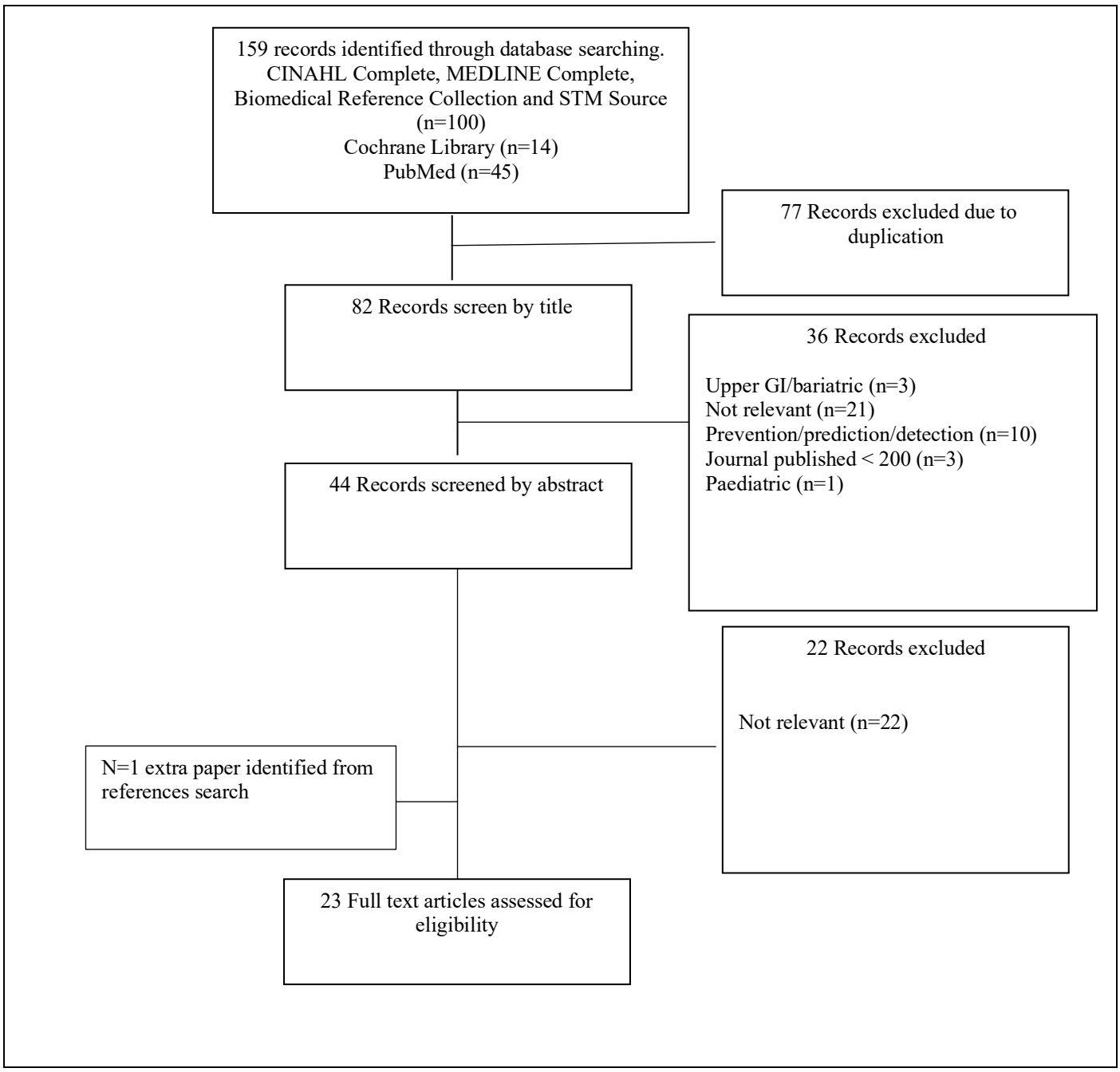
Excluded studies

List any excluded studies below. These are studies that were initially considered for inclusion at the level of full text review, but were later excluded for specific reasons.

Author	Title	Exclusion reason	Company comments
(Ammann et al. 2019)	"A dual-perspective analysis of the hospital and payer-borne burdens of selected in-hospital surgical complications in low anterior resection for colorectal cancer."	Economic analysis in USA $	Interesting differences in AL and no AL cost from USA. However not NHS data
(Bugiantella et al. 2017)	Cost-effectiveness analysis of the temporary percutaneous ileostomy for faecal diversion after colorectal resection in elderly	Economic analysis in Euro. No AL data	
(Floodeen et al. 2017)	Costs and resource use following defunctioning stoma in low anterior resection for cancer - A long-term analysis of a randomized multicenter trial	Economic analysis in Euro.	
(Frye et al. 2009)	Anastomotic leakage after resection of colorectal cancer generates prodigious use of hospital resources	No economic analysis	Impact of AL on hospital treatments recorded.
(Hammond et al. 2014)	The burden of gastrointestinal anastomotic leaks: an evaluation of clinical and economic outcomes	Economic analysis in USA $	Interesting differences in AL and no AL cost from USA. However not NHS data
(Kang et al. 2013)	Risk factors for anastomotic leakage after anterior resection for rectal cancer.	Economic analysis in USA $	Interesting differences in AL and no AL cost from USA. However not NHS data
(Kim, Jung, and Kim 2019)	Ileostomy versus fecal diversion device to protect anastomosis after rectal surgery: a randomized clinical trial	No economic analysis	
(Koperna 2003)	Cost-effectiveness of defunctioning stomas in low anterior resections for rectal cancer: a call for benchmarking.	Economic analysis in Euro.	
(La Regina et al. 2019)	Financial Impact of Anastomotic Leakage in Colorectal Surgery	Economic analysis in Euro.	Interesting differences in AL and no AL cost from Eurpoe. However not NHS data
(Lee, Gregory, and Cool 2019)	Clinical and economic burden of colorectal and bariatric anastomotic leaks	Economic analysis in USA $	Interesting differences in AL and no AL cost from USA. However not NHS data
(Lim et al. 2012)	PSU15 Clinical and Economic Burden of Anastomotic Leaks After Colorectal Surgeries	Economic analysis in USA $	Interesting differences in AL and no AL cost from USA. However not NHS data
(MacDermid et al. 2014)	Decision-making in rectal surgery	No economic analysis	
(Nelson et al. 2018)	Early versus conventional stoma closure following bowel surgery: A randomized controlled trial	No economic analysis	

(Ribeiro et al. 2019)	The Clinical and Economic Burden of Colorectal Anastomotic Leaks: Middle-Income Country Perspective	Economic analysis in Brazilian $	Interesting differences in AL and no AL cost from Brazil. However not NHS data
(Robertson et al. 2015)	Cost analysis of early versus delayed loop ileostomy closure: a case-matched study	Economic analysis in Newzeland $	
(Roy, Ghosh, and Yoo 2015)	An Assessment of the Clinical and Economic Impact of Establishing Ileocolic Anastomoses in Right-Colon Resection Surgeries Using Mechanical Staplers Compared to Hand-Sewn Technique	Economic analysis in USA $	Interesting cost analysis from USA.
(Scarborough et al. 2017)	Associations of Specific Postoperative Complications With Outcomes After Elective Colon Resection: A Procedure-Targeted Approach Toward Surgical Quality Improvement	No economic analysis	Impact of AL on hospital treatments recorded.
(Stey et al. 2014)	Outcomes and cost of diverted versus undiverted restorative proctocolectomy	Economic analysis in USA $. Not looking at impact of AL	
(Turrentine et al. 2015)	Morbidity, mortality, cost, and survival estimates of gastrointestinal anastomotic leaks	Economic analysis in USA $.	Interesting differences in AL and no AL cost from USA. However not NHS data
(Wu et al. 2017)	Temporary Diverting Stoma Improves Recovery of Anastomotic Leakage after Anterior Resection for Rectal Cancer.	No economic analysis	

Report the numbers of published studies included and excluded at each stage in an appropriate format (e.g. PRISMA flow diagram).



Appendix E: Checklist of confidential information

Please see section 1 of the user guide for instructions on how to complete this section.

Does your submission of evidence contain any confidential information? (please check appropriate box):

No ☐ If no, please proceed to declaration (below)

Yes ☒ If yes, please complete the table below (insert or delete rows as necessary). Ensure that all relevant sections of your submission of evidence are clearly highlighted and underlined in your submission document, and match the information provided in the table. Please add the referenced confidential content (text, graphs, figures, illustrations, etc.) to which this applies.

Page	Nature of confidential information	Rationale for confidential status	Timeframe of confidentiality restriction
55 and 67	☒ Commercial in confidence ☐ Academic in confidence	Annual cost of stoma care calculated at [redacted]. Based on Tableau data March2018-Feb2019 *[redacted] and NHS DAC data of [redacted] Jan-June 2019– data purchased by company not believed to be in public domain.	Not Sure
Details	Enter text.		
56	☒ Commercial in confidence ☐ Academic in confidence	PCA stoma accessories [redacted] per patient based on PCA data Jan-March 2019 [redacted] and year estimate of [redacted] Data purchased not believed to be public.	Enter text.
Details	Enter text.		
57, 66 and 67	☒ Commercial in confidence ☐ Academic in confidence	Average cost of percutaneous drain [redacted]. Based on NHSSC data	

Confidential information declaration

I confirm that:

- all relevant data pertinent to the development of medical technology guidance (MTG) has been disclosed to NICE
- all confidential sections in the submission have been marked correctly
- if I have attached any publication or other information in support of this notification, I have obtained the appropriate permission or paid the appropriate copyright fee to enable my organisation to share this publication or information with NICE.

Please note that NICE does not accept any responsibility for the disclosure of confidential information through publication of documentation on our website that has not been correctly marked. If a completed checklist is not included then NICE will consider all information contained in your submission of evidence as not confidential.

Signed*: ** Must be Medical Director or equivalent*		**Date:**	February 4, 2020
Print:	Dr. Ricard Rosique Gastrointestinal Surgeon	**Role / organisation:**	Head Medical Scientific Affairs Center of Excellence Closure Technologies
Contact email:	ricard.rosique@bbraun.com		

NICE National Institute for Health and Care Excellence

Medical technologies guidance

Collated expert questionnaires

Technology name & indication: **Endo-SPONGE for colorectal anastomotic leakage**

Experts & declarations of interest (DOI)

Expert #1	Mr Edmund Leung, Consultant Colorectal Surgeon, Hereford County Hospital
	DOI: None
Expert #2	Mr Biju Aravind, Consultant Colorectal Surgeon, East Kent Hospitals NHS Foundation Trust
	DOI: None
Expert #3	Dr Anandapuram Deepak Dwarakanath, Consultant physician and medical director, North Tees and Hartlepool NHS Foundation Trust
	DOI: None
Expert #4	Mr Andrew Day, Consultant General and Colorectal Surgeon, Surrey and Sussex Healthcare NHS Trust
	DOI: NONE
Expert #5	Mr Jim Khan, Consultant Colorectal & Robotic Surgeon, Portsmouth Hospitals NHS Trust
	DOI: NONE
Expert #6	Dr James Turvill, Consultant Gastroenterologist, York Teaching Hospital NHS Trust
	DOI: NONE
Expert #7	Mr Mark Cheetham, Consultant Surgeon and Care Group Medical Director, Shrewsbury and Telford NHS Hospital Trust
	DOI: None

How NICE uses this information: the advice and views given in these questionnaires are used by the NICE medical technologies advisory committee (MTAC) to assist them in making their draft guidance recommendations on a technology. It may be passed to third parties associated with NICE work in

accordance with the Data Protection Act 2018 and data sharing guidance issued by the Information Commissioner's Office. Expert advice and views represent an individual's opinion and not that of their employer, professional society or a consensus view (unless indicated). Consent has been sought from each expert to publish their views on the NICE website.

1. **Please describe your level of experience with the technology, for example: Are you familiar with the technology? Have you used it? Are you currently using it? Have you been involved in any research or development on this technology? Do you know how widely used this technology is in the NHS?**

Expert #1	I am familiar with endosponge and have used it in times of need. I have never been involved in the research nor development of this product. It is used in many NHS centres
Expert #2	I have substantial experience with the use of Endo-sponge for the last 5 years with 3 different patients. I have recently used endo-sponge on a patient who developed a leakage of an anastomosis 5 years following his initial rectal surgery. His leakage and related sepsis resulted in necrotising fasciitis down his leg which needed multiple surgeries. The site of leakage was controlled through this phase with a proximal defunctioning stoma and endo-sponge in the cavity. After initial inpatient management, in the later phases was done as an outpatient procedure. This carried for months before he was fit for a definitive surgery of resection of the rectum with the anastomosis. I have not been involved in research with this device nor have any other conflict of interest. I was aware of the system from a Hospital where I trained as a Higher Surgical trainee more than 7 years back and know of a few hospitals where they are used.
Expert #3	I AM AWARE OF THE TECHNOLOGY NO NO NO

	NO
Expert #4	I am familiar with the technology, but I have never used it or seem it used in the clinical setting. I am unaware of any of my colleagues using the technology in the surrounding hospitals, and I was never exposed to it during my registrar training within the region. I have not been involved in the research and development of the product.
Expert #5	I am familiar with the technology and have used it in selected patients. I have this available in my hospital. I have not been involved in any research around the usage and development of this technology. I have a fair idea of its uptake across the country due to my involvement with teaching and training and examining at the Royal College
Expert #6	I am aware of the technology but have not used it myself. Negative pressure wound therapy is a well established treatment. My colleagues have been discussing the use of endo-SPONGE for oesophageal leak. Having spoken to surgical colleagues the endo-SPONGE is available/approved for use by the Trust. It has been used occasionally and successfully for colorectal anastomotic leaks in the last few years. I have not been involved in any research using this technology. I do not know how widely it is used across the wider NHS.
Expert #7	I am familiar with Endosponge and have used it sporadically since It came to market. I am currently using it is selected patients. I had some experience of using a prototype of Endosponges in an open label trial in 2004/ 2005 at St Mark's Hospital

2. Has the technology been superseded or replaced?

Expert #1	Not aware
Expert #2	Not to my knowledge
Expert #3	NOT TO MY KNOWLEDGE. NOVEL CONCEPT
Expert #4	Not that I am aware of
Expert #5	Not to my knowledge
Expert#6	No
Expert#7	No

Current management

3. How innovative is this technology, compared to the current standard of care? Is it a minor variation or a novel concept/design?

Expert #1	It enhances recovery for those who have a colorectal anastomotic leak
Expert #2	It is ideal to manage extra peritoneal rectal anastomotic leakage when it can be accessed by trananal route, ie low rectal anastomotic leakage with contained leakage causing sepsis. I will class it as a significant variation of current standard of care for a selected group of patients in the above category and avoids technically difficult repeated transanal or radiological drainage and extensive surgery in an already sick patient.
Expert #3	INNOVATIVE STEP FORWARD IN CARE
Expert #4	It is a novel concept that has been around for approximately ten years

Expert #5	Minor variation
Expert#6	The endo-SPONGE represents an innovative technology: alternatives are de-functioning surgery, percutaneous or trans-anastomotic drainage or TPN.

4. Are you aware of any other competing or alternative technologies available to the NHS which have a similar function/mode of action to the notified technology? If so, how do these products differ from the technology described in the briefing?

Expert #1	Not known to be effective.
Expert #2	I am not aware of any other technology or variations.
Expert #3	No
Expert #4	I am not aware of any other marketed products, although there are a number of case reports of self-made 'Endo-Sponges' within the literature.
Expert #5	No
Expert#6	No
Expert#7	No

Potential patient benefits

5. What do you consider to be the potential benefits to patients from using this technology?

Expert #1	Enhanced recovery, reduced morbidity by less discharge or pain
Expert #2	1. It is beneficial for a group of patients who had a low rectal anastomosis and subsequent leakage without peritonitis.

	2. It will reduce the requirement for immediate major surgery at a time when the patient is most unwell as an aftermath of the sepsis from the leakage. 3. It provides enough time to build up the patients' nutrition and physical health with control of sepsis and plan a procedure if required.
Expert #3	LESS RE-OPERATION LESS COLOSTONY FORMATION
Expert #4	Anastomotic leak following low anterior resection is a complication (approximately 10% of this cohort of patients) with considerable morbidity for patients that can ultimately lead to an inability to restore bowel continuity, outside of the immediate complications. If this technology can lead to a closure of the leak with minimal inconvenience to the patient, there are potentially clear advantages.
Expert #5	Control of infection Healing of infected areas
Expert#6	Largely spares the need for de-functioning surgery
Expert#7	Better control of pelvic infection Quicker treatment Reduction in permanent stoma rates

6. Are there any groups of people who would particularly benefit from this technology?

Expert #1	Only those with large low / mid-rectal anastomotic leak, not colo-anal anastomosis
Expert #2	As mentioned before, leakage of extraperitoneal low or mid rectal anastomosis with localised sepsis are the most ideal patients

Expert #3	FRAILER PATIENTS
Expert #4	Anastomotic leak post low anterior resection with a defunctioning ileostomy
Expert #5	Patients who develop complications after surgery such as anastomotic leak after bowel resection
Expert #6	All patients in the context of colorectal anastomotic leakage where there is not a generalised peritonitis, that is, where the leak is contained in the pre-sacral cavity. Frailer patients in whom a second (de-functioning) operation would carry significant co-morbidity might particularly benefit from the endo-SPONGE.
Expert #7	Patients having a low anterior resection, Hartmann's procedure or ileoanal pouch who have developed a localised anastomotic leak

7. Does this technology have the potential to change the current pathway or clinical outcomes? Could it lead, for example, to improved outcomes, fewer hospital visits or less invasive treatment?

Expert #1	I think it has already demonstrated earlier recovery, not fewer visits but less invasive treatment.
Expert #2	In this particular group of patient, the current pathway suggested in the joint ASGBI-ACPGBI publication ' Issues in professional practice, Prevention, diagnosis and management of colorectal anastomosis' publishes March 2016, use of endosponge will come under source control for case scenario 1 and 2a in extraperitoneal anastomotic leakage (pg 22) This will certainly benefit the above group of patients and improve outcome, and in my cases, reduce prolonged hospital stay. In my cohort they still required further surgery although at a later date on an elective basis vastly improving their survival and QOL.
Expert #3	YES, LESS RE-OPERATION QUICKER RECOVERY TIMES LESS HOSPITAL VISITS

Expert #4	It could lead to less invasive treatment being required- ie further surgery with possible end colostomy formation.
Expert #5	this may reduce the need to re-operate on these patients but a the cost of inpatient treatment and frequent dressing changes
Expert #6	Yes, it is a less invasive treatment and could improve clinical outcomes but may not reduce inpatient time. The endo-SPONGE can sometimes be managed as an outpatient. But patient selection is important. This is a time consuming technology. It has a learning curve and requires training
Expert #7	Yes it could lead to a reduction in length of stay and a reduced need for a repeat abdominal operation

Potential system impact

8. What do you consider to be the potential benefits to the health or care system from using this technology?

Expert #1	Allows early heal and earlier reversal of the patient's ileostomy
Expert #2	It contributes to the management of a difficult and complex group of patient who had a complication following long procedure like low anterior resection usually for a cancer. It reduces the need for another immediate prolonged surgery in an already unwell patient and give a very vital source control of the anastomotic leakage hence improving outcomes. It might also reduce the requirement for permanent stoma in such cases as the alternative option may include a major surgery and taking down the anastomosis resulting in permanent stoma and resulting reduced QOL.
Expert #3	LESS MORBIDITY AND MORTALITY FASTER RECOVERY
Expert #4	Easy and simple to use.

	Allows restoration of bowel continuity and closure of the ileostomy. Therefore, no requirement for ongoing stoma management and appliances.
Expert #5	Costs of reoperation may be reduced
Expert #6	This is a niche product. Publications include small numbers of patients. We have used it 3 times in 4 years at our Trust. So benefits for a care system I suspect would be marginal. For the individual patient endo-SPONG provides a safe, effective mechanism of salvaging a colorectal anastomosis. This would have significant benefits in terms of morbidity and perhaps mortality.
Expert #7	Reduction in permanent stoma with a reduction in costs associated with stoma appliances

9. Considering the care pathway as a whole, including initial capital and possible future costs avoided, is the technology likely to cost more or less than current standard care, or about the same?

Expert #1	A bit more and can be labour intensive
Expert #2	Its benefits far outweigh the current standard of care in this group of patients. In my patients, it gave excellent control over sepsis and I was able to discharge them from the hospital once their health improved following which they were able to have planned definitive surgery. In my experience it may be argued that it cost less in ITU and inpatient stay as we get better control of sepsis quicker and discharge from hospital. However there are cost implications to continuing review of patient in the OPD or endoscopy suite as required until the healing is complete. If the management results in avoiding a permanent stoma this will have huge financial and logistical saving for the NHS and QOL for patient.
Expert #3	REDUCE COSTS, AS LIKELY TO BE LESS OPERATIONS
Expert #4	The current standard of care is to wait for a number of months to allow the leak to close on its own. These patients will require to continue managing their ileostomy with stoma bags, so there could be a potential cost saving.

Expert #5	This may be cost effective in the long term however no such data exists at present
Expert #6	I would estimate about the same.
Expert #7	It is difficult to assess the cost effectiveness of this technology. There is likely to be a trade-off between repeated procedures to change the Endosponge and the longer term usage of stoma supplies. This may vary dependent of whether the patients is kept as an inpatient for the duration of Endosponge or not

10. What do you consider to be the resource impact from adopting this technology? Could it, for example, change the number or type of staff needed, the need for other equipment, or effect a shift in the care setting such as from inpatient to outpatient, or secondary to primary care?

Expert #1	Need to train district nurses, patient, ward nurses and doctors who have to change the pack
Expert #2	The decision for its use and appropriateness has to be assessed and decided by an experienced colorectal Consultant, ideally with experience in using them. Once it is assessed and deemed appropriate, then it can be deployed by medical gastroenterologist or colorectal surgeon. Logistically it is possible to deploy the endosponge in an inpatient, outpatient, in theatre or in endoscopy suite settings. I found the system easy to deploy and change in an outpatient setup. I was able to train an SCP (Surgical care practitioner) to use them with very good results in the care of one of my patients. We will also have o consider radiological signs of resolution like CT or MRI scans.
Expert #3	PURCHASE AND TRAINING OF USE OF ENDO-SPONGE REDUCED IN PATIENT STAY
Expert #4	If this technology were to be used routinely it would require a service to be set up. The sponges need to be changed every 48-72hrs in endoscopy, which would require space on lists and specific endoscopists with the skill set to manage them. It may take up to a month to achieve closure of the defect, necessitating multiple hospital visits.
Expert #5	Blank

Expert #6	The numbers will always be small. I suspect a surgical ward would cope well with this as it does negative pressure wound therapy. The endo-SPONGE is deployed endoscopically and then placed under suction. Every three days it needs to be replaced; a further endoscopy is required. This cycle repeats itself often for over a month until there is healing. Arguably one could shift from in- to out-patient management but staff, training, endoscopy and time are all required in a co-ordinated way.
Expert #7	Possible shift costs from primary care (stoma supplies provision) to secondary care (theatres or endoscopy costs)

11. Are any changes to facilities or infrastructure, or any specific training needed in order to use the technology?

Expert #1	Learn to apply and remove. Learn to manage in community if it starts to flash red light
Expert #2	As above I found it easy to understand and use. However, I emphasise that the appropriateness of its use has to be assessed by an experienced colorectal surgeon. It also needs monitoring as to the amount of output and requirement for gradual reduction in the size of the sponge to be cut before deployment. I will suggest that the technology should be known to wider colorectal consultants undertaking rectal surgery, and they be offered training for assessing and using the technology. It will be useful to have regional champions to facilitate and help monitor their use. As it is not a common occurrence to have a low rectal anastomosis leakage (less than 1 in 10), there has to be resources available to remind the surgeons of the options in such difficult situation.
Expert #3	NO
Expert #4	There would be training required for the endoscopist and the endoscopy nurses. In addition, the colorectal nurse specialists would have to be aware of how to manage the system in the community.
Expert #5	The professional dealing with this will ned an update and hands on training however its not very extensive
Expert #6	Yes, training and organisational infrastructure if outpatient care is offered.
Expert #7	Need for training in the usage of Endosponge

12. Are you aware of any safety concerns or regulatory issues surrounding this technology?

Expert #1	Not really. Non healing may still occur. Anastomotic stricture
Expert #2	A concern was reported to the MHRA from my cohort of patients.

	The lubricant gel which accompanied the kit has a white ring around its neck which comes loose when the gel is opened. We suspect this ring stuck to the sponge or found its way into the tube which is used to deploy the sponge into the abscess cavity. This small ring was found in the pelvic abscess cavity at a later time during definitive surgery. I have reported this to the company and to MHRA. It is informed that the design of the lubricant gel tube is replaced with one without a loose ring as per the representative from B Braun in the last communication I have received.
Expert #3	NO
Expert #4	As the device uses a low-pressure vacuum there is a theoretical risk of developing a small bowel fistula.
Expert #5	No, the dressings may cause some fibrosis and scaring which may result in poor bowel function afterwards but again data is limited on this account
Expert #6	The endo-SPONGE can be mal-deployed causing bleeding and fistulation. I believe this to be rare.
Expert #7	There is a theoretical risk of developing a fistula between the small bowel and the rectum (especially when Endosponge is used after a Hartmann's procedure)

General advice

13. Please add any further comments on your particular experiences or knowledge of the technology, or experiences within your organisation.

Expert #1	I find it with good outcome for the few with large anastomotic leak
Expert #2	I had 3 cases who had benefited from endosponge in the last 5 years. Of the three cases, two had a low rectal extraperitoneal anastomotic leakage. One of these 2, had necrotising fasciitis from this sepsis, spreading down his leg. The third case was after a subtotal colectomy and subsequently developed pelvic sepsis at the end of the residual rectal stump which was again extra peritoneal and was accessible by transanal route.

	All 3 cases had source control of sepsis with endosponge and then required definitive elective surgery after control of their sepsis, two had APER and one had a rectal stump excision. Interestingly, one of them had initial leakage of anastomosis 5 years back at another hospital which completely healed with endosponge treatment which saved him from a permanent stoma. Unfortunately, 5 years on, he developed sepsis from the same site which I managed with endosponge and an APER. I was able to use a surgical assessment unit at our hospital, where a nursing team is at hand to help with dressings and basic surgical requirements are met for such a procedure.
Expert #3	NIL
Expert #4	N/A
Expert #5	It's a good way of controlling infection after the leak from the bowel anastomosis however does require an anaesthetic for the dressing to be placed and then changed every 3-5 days whiohc means that the patient has to stay in hospital. The healing is quicker and less infection but the r is a concern of scarring caused by this which may result in bad bowel function long term
Expert #6	The experience has been positive on a small, selected group of patients. It is time consuming to use.
Expert #7	Nil

Other considerations

14. Approximately how many people each year would be eligible for intervention with this technology, either as an estimated number, or a proportion of the target population?

Expert #1	2

Expert #2	I have managed 3 cases in 5 years, while I average circa 40-50 colorectal resections per year of which about 30% or more could be rectal resections
Expert #3	NOT SURE OF THE NUMBERS
Expert #4	If 10% of low anterior resections leak, in a district general hospital operating on approximately 20-25 rectal cancers in the mid to low rectum. Potentially there could be 2-3 patients per year per trust, with an average volume, that would be applicable.
Expert #5	The incidence of leaks is about 5-6|% of the operated cases in rectal cancer surgery so we are talking of 10-20 patients per million approx
Expert #6	Very much an estimate, but in the order of 100 patients per year in England, for this specific indication.
Expert #7	Nil

15. Would this technology replace or be an addition to the current standard of care?

Expert #1	Addition to existing care
Expert #2	Current pathway suggested in the joint ASGBI-ACPGBI publication ‘ Issues in professional practice, Prevention, diagnosis and management of colorectal anastomosis’ publishes March 2016, use of endosponge will come under source control for case scenario 1 and 2a in extraperitoneal anastomotic leakage (pg 22 of the document). As per this pathway it is the preferred way for source control in such situation.
Expert #3	IN ADDITION TO CURRENT CARE
Expert #4	It would be an addition
Expert #5	Yes
Expert #6	Additional

Expert #7	Replace for some patients

16. Are there any issues with the usability or practical aspects of the technology?

Expert #1	No
Expert #2	None other than the concern I have raised already. Despite the technology being around for several years, the sporadic nature of anastomotic leakage and relative lack of publicity of the device has hindered good quality research and an algorithm which will help new users to the device. I am hoping the guidance from NICE will change this scenario.
Expert #3	NO
Expert #4	The frequent regular changes of the sponge could place logistical difficulties on an already over stretched endoscopy service.
Expert #5	No
Expert #6	Training (not onerous) and time
Expert #7	Access to endoscopy or theatre suites for repeated visits Feasibility of endoscopic approach

17. Are you aware of any issues which would prevent (or have prevented) this technology being adopted in your organisation or across the wider NHS?

Expert #1	Learning curve, funding, staffing issues
Expert #2	Lack of awareness of the device and sporadic nature of low rectal anastomotic leakage are the reasons as I mentioned above.

	I feel that most colorectal units will have the required logistical support for the use of the endosponge device.
Expert #3	NO
Expert #4	No
Expert #5	No
Expert #6	No
Expert #7	Cost of consumables Access to consumables in an emergency

18. Are you aware of any further evidence for the technology that is not included in this briefing?

Expert #1	No
Expert #2	Th efollwoing 2 publications are from the later half of 2019. Effectiveness of endosponge therapy for the management of presacral abscesses following rectal surgery. Huisman JF, van Westreenen HL, van der Wouden EJ, Vasen HFA, de Graaf EJR, Doornebosch PG, Tang TJ, Schot I, Brohet RM, de Vos Tot Nederveen Cappel WH, Vermaas M. Tech Coloproctol. 2019 Jun;23(6):551-557. doi: 10.1007/s10151-019-02007-9. Epub 2019 Jul 23. Endoluminal negative pressure therapy in colorectal anastomotic leaks. Popivanov GI, Mutafchiyski VM, Cirocchi R, Chipeva SD, Vasilev VV, Kjossev KT, Tabakov MS.

	Colorectal Dis. 2019 Jul 5. doi: 10.1111/codi.14754. [Epub ahead of print] Review.
Expert #3	NO
Expert #4	No
Expert #5	No
Expert #6	No
Expert #7	No

19. Are you aware of any further ongoing research or locally collected data (e.g. audit) on this technology? Please indicate if you would be able/willing to share this data with NICE. Any information you provide will be considered in confidence within the NICE process and will not be shared or published.

Expert #1	No, happy to share this with NICE process
Expert #2	None to my knowledge
Expert #3	NO; N/A
Expert #4	I am unaware of any ongoing national audits
Expert #5	No
Expert#6	No
Expert#7	No

20. Is there any research that you feel would be needed to address uncertainties in the evidence base?

Expert #1	Numbers are not great to perform RCT so small pilot prospective cohort study

Expert #2	I believe an algorithm for use of endosponge might help the uptake of the device for such cases. It will be interesting to know how many of the low rectal resections with leakage could potentially managed with endosponge which are currently resulting in permanent stoma.
Expert #3	NO
Expert #4	Reviewing the available evidence on PubMed, there are a number of published case series with small numbers showing promising results. However, there are no randomised studies comparing the technology to the current standard. Therefore caution must be used in adopting this technology, there is a good argument to recommend a national study be conducted.
Expert #5	Looking at the efficacy and safety profile of endosponge And the cost effectiveness model
Expert #6	No
Expert #7	Cost effectiveness of Endosponge

Declaration of interests

Description of Interest	Date Interest arose	Date Interest ceased

Please see over the page information on how to complete the above boxes

The information you provide on this form will be used to assess if you have any potential conflicts of interest, we ask for this information to comply with our organisational policies.

Information may be disclosed to third parties in accordance with the Freedom of Information Act 2000 and will be published in registers that NICE holds.

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I confirm that the information provided above is complete and correct. I acknowledge that any changes in these declarations during the course of my work with NICE, must be notified to NICE as soon as is practicable and no later than 28 days after the interest arises. I am aware that if I do not make full, accurate and timely declarations this may result in potential disciplinary action if there has been a deliberate breach of the policy.

I do / do not [delete as applicable] give my consent for this information to be published on the registers that NICE holds. If consent is NOT given, please give reasons below: (please note this will be agreed in exceptional cases only).

Reason for non-disclosure: Enter text here.

Signed (employee): Enter text here. **Date:** Enter text here.

HOW TO COMPLETE THE DECLARATION OF INTEREST FORM

Name & role: Insert your name, your role and employer within the NHS.

Description of Interest: Provide a description of the interest that is being declared. This should contain enough information to be meaningful to enable a reasonable person with no prior knowledge to be able to read this and understand the nature of the interest.

Types of interest: **Financial interests -** where a person gets direct financial benefit.

Non-financial professional and personal interests - Where a person has role relevant to NICE's work from which they do not receive a financial benefit. This includes:

- holding office or a position of authority in a professional organisation such as a Royal College, a university, charity, advocacy group or any other organisation in the health, public health or care sector
- holding a position of authority in an organisation contracting for services with NICE.

Indirect interests - where there is, or could be perceived to be, an opportunity for a third party closely associated with the board member or employee to benefit.

A benefit may arise from both a gain or avoidance of a loss.

Relevant Dates: Detail here when the interest arose and, if relevant, when it ceased.

NICE National Institute for Health and Care Excellence

External Assessment Centre correspondence log: instructions for EAC

Please use this table to record any questions or clarifications sent to the company, expert advisers and organisations/individuals outside of NICE.

Example:

#	Date	Who / Purpose	Question/request	Response received
1.	12/04/2018	**Manufacturer** Initial questions	Can you explain the origin of the included studies i.e. in which database were they found?	The origin of the included studies was pubmed.
2.	12/04/2018	**Manufacturer** Initial questions	Can you provide a rationale for the date limits used?	A 10-year range was decided upon to capture evidence related to the field of cardiology rather than the intervention itself.
3.	12/04/2018	**Manufacturer** Initial questions	Can you explain how the pubmed database was searched i.e. which limits were applied?	This search was completed in January 2018 and was restricted to titles and abstracts. For please see the export files, and the xls export sheet used to select the studies. **Files included in Appendix 1**.
4.	05/05/2018	**Expert – Dr C Smith (consultant cardiologist)** Surgical questions	What are the risks of Transcathetar Aortic Value replacement (TAVR)?	Some of the main risks of an aortic valve replacement include wound, lung, bladder or heart valve infections, blood clots, strokes, arrhythmia and reduced kidney function for a few days.

NICE National Institute for Health and Care Excellence

External Assessment Centre correspondence log

MT461 Endo-sponge for treating colorectal anastomotic leakage

The purpose of this log is to show where the External Assessment Centre relied in their assessment of the topic on information or evidence not included in the company's original submission. This is normally where the External Assessment Centre:

a) become aware of additional relevant evidence not submitted by the company;
b) needs to check "real world" assumptions with NICE's expert advisers, or;
c) needs to ask the company for additional information or data not included in the original submission, or;
d) needs to correspond with an organisation or individual outside of NICE

These events are recorded in the table to ensure that all information relevant to the assessment of the topic is captured. The table is shared with the NICE medical technologies advisory committee (MTAC) as part of the committee documentation, and is published on the NICE website at public consultation.

#	Date	Who / Purpose	Question/request	Response received
X.	*XX/XX/XXXX*	*Who was contacted? (if an expert, include clinical area of expertise)* *Why were they contacted? (keep this brief)*	*Insert question here. If multiple questions, please break these down and enter them as new rows*	*Only include significant correspondence and attach additional documents/graphics/tables in Appendix 1, citing question number*
1.	15/01/2020	BBraun	Telephone call with Company and NICE to discuss get clarity on some issues, primarily related to the technology, how it works, and suitable populations.	Detailed notes attached (See appendix 1: File attachments/additional information from question 1:

2.	27/01/2020	BBraun	E-mail to confirm the CE marking of Endo-SPONGE due to a discrepancy between the scope, MIB and company submission	It was an error on the original submission, Endo-SPONGE is class IIb device
3.	29/01/2020	BBraun	Follow up e-mail on CE marking as company response was different to their submission	It is a class IIa as the DoC says, when you asked previously I looked at the CE cert which covers all our Wound Closure portfolio and mistakenly read is as IIb
4.	06/03/2020	BBraun	E-mail to company regarding two references used in the economic submission. The reference links don't work, can we check the source please?	Reply received 11/03/2020 Company provided the reference links.
5.	17/01/2020	Clinical Experts	A number of additional questions covering clinical pathways, pain relief (the use of anaesthetics), the comparator, the use of the technology in clinical practice)were sent to clinical experts and responses received from 3 experts (These are attached below).	Files 3 to 5 attached
6.	17/02/2020	Clinical Expert	Telephone call with a clinical expert to discuss Endo-SPONGE in more detail including clinical pathway, indication, contraindication, the length of the procedure, long-term survival, and the clarity of the difference between stoma/ileostomy reversal and restoration of bowel continuity).	Notes from call attached
7.	27/02/2020	Clinical Expert	Telephone call with a clinical expert to discuss Endo-SPONGE in more detail including the grading system for anastomotic leak, the definition of chronic and acute leakage, contraindication, clinical parameters for the economic modelling such as the length of the procedure, the use of anaesthetics and staff level	Notes from call attached – please not these notes have **NOT** been verified by the clinical expert as accurate.

8.	12/03/2020	Clinical Expert	A telephone call was originally arranged for 20/02/2020 however there were problems with the call. A follow-up list of questions was sent to this expert.	Response received 12/03/2020 which was after the submission date for the final report. These responses are included below but have not been included in the EAC report.

Insert more rows as necessary

Appendices.

During correspondence with the company and experts, additional information is sometimes included as file attachments, graphics and tables. Any questions that included additional information of this kind is added below in relation to the relevant question/answer:

Appendix A: File attachments/additional information from question 1

Cedar
Healthcare Technology Research Centre

Questions for Company (B Braun)

Topic	Endo-SPONGE for treating colorectal anastomotic leakage (MT461)
Date sent	13th January 2020

	Company Submission Page Number (section)	EAC Question	Company Response
1	3 (decision problem)	Antibiotics are listed as both a comparator and an outcome. Could the company clarify whether this is because patients may be initially treated with endo-sponge and antibiotics?	Use of antibiotics will be an individual clinician decision and largely dependent on the patient and severity of condition Treatment options: • Antibiotics alone • Antibiotics + conservative management (inc. endo-sponge) • Antibiotics + surgical management
2		In the event that a patient required antibiotics, would patients initially managed using endo-sponge have antibiotics added to their treatment (endo-sponge + antibiotics) or would treatment be sequential (endo-sponge followed by antibiotics) **EAC Note:** This appears to be addressed on page 12 (Non-surgical intervention) where it states that antibiotics may be used alone or in combination with percutaneous drainage) suggesting possible treatment combinations of: • Antibiotics alone • Percutaneous drainage alone • Antibiotics + percutaneous drainage • Percutaneous drainage followed by antibiotics if required	As above. Endo-sponge is considered to be a non-surgical intervention by the company. The majority of patients do not require sedation, some will require mild sedation. The company opinion is that a very small number of patients would undergo an operative procedure in a theatre setting with general anaesthetic. Majority of patients can be seen in the endoscopy suite or as outpatients. The company acknowledges that the literature does include patients who have endo-sponge operatively.

	Company Submission Page Number (section)	EAC Question	Company Response
3	4 (the technology)	Could the company give a brief overview of how the technology works in practice? For example, would a pack of 10 or 5 be required for each patient?	Average of 7-10 sponges per patient depending on cavity size Sponge inserted and attached to an external vacuum bottle (2 settings on the bottle, company state (IFU) that the second setting should not be used. Each individual kit in a pack is wrapped and sterile with a 5 year shelf life Patients can be either inpatient or outpatient and this will largely be dependent on the severity of the patient condition and clinical decision on the best way to manage the anastomotic leak. Some patients may be kept in for long enough for treatment to be confirmed working then treated as outpatients. The company states that a pack of 10 or 5 contains each individual wrapped kit. One kit contains one sponge, a pack of 5 kits would have 5 separate sponges. There is pressure button on the top of vacuum bottle, including on and off, and option 1 and 2 (applying different pressure). Only option 1 should be used, option 2 is too strong a vacuum.
		Are any parts of the system reusable?	None of the kit is re-useable. The components in the kit are single use.
		How is the sponge resized through the course of treatment or are sponges available in different sizes separately?	Endoscopist/Surgeon will check the cavity size to determine what size sponge is required When previously used sponge is removed, its size can be used as a reference for the next sponge. Sponge can be cut (sides, top or both) to size
		How are multiple sponges placed within the cavity?	Large cavities, up to 3 sponges can be used. 2 sponges can be attached to one bottle but 3rd sponge will require an additional vacuum bottle

	Company Submission Page Number (section)	EAC Question	Company Response
4	10	Point of clarity This section states the sponge system is changed every 48-72 hours. The EAC note that the MIB states every 24 to 72 hours. Could the company clarify which timings are accurate?	Clinicians often remove the initial sponge after 24 hours to check if treatment is working. They will inspect the cavity after the sponge is removed. After 72 hours the sponge can become difficult to remove as it promotes healing and can begin to 'grow' around the sponge. Also, effectiveness of the sponge is reduced. It is likely that different clinical teams will see the same patient for insertion/change of sponge(s).
5	14 & 15	Could the company clarify that Endo-sponge would replace current non-operative methods? **EAC note:** This goes back to the query about antibiotics? Are antibiotics considered a non-operative intervention or are they used in addition to other non-operative methods (endoscopic clips, fibrin glue etc)?	The company consider that endo-sponge would be a viable alternative to all non-operative and operative interventions apart from antibiotics. I believe we mentioned that in the literature we used, we saw that Endo-SPONGE was being used successfully in anastomotic leaks that were up to 270 degrees around, which is extremely severe. The intention is for endo-sponge to come in early in the clinical pathway to prevent/reduce antibiotic use.
6	18 (Training)	Could the company indicate whether they consider there to be any risks associated with not routinely providing training in clinical practice?	• The company deliver group presentations/demonstrations to MDTs/clinicians • Additional training can be provided if necessary on a request basis • Product can be purchased without training but any new customers are contacted by the company • Procedure would always be performed by an endoscopist/surgeon • The team from company is assisting during the first procedure performed by the new client.

	Company Submission Page Number (section)	EAC Question	Company Response
		Is there an additional cost for hands on training?	No additional training costs
		Does the company have any details on the number of users who request more hand on training?	Minimal to zero
7	19-22	Please confirm the number of included studies (Table on p19 states 20, Table 1 includes 21 studies)	Company state 20 however acknowledge there are some errors in the data and requested to send an updated version. This has been agreed by NICE and EAC provided the content/conclusions do not change and that all corrections are clearly marked (tracked changes/comments box) for comparison against original submission
8	67 (Complaints)	% complaints for 9 months of 2019 is higher than in previous years. Could the company comment on this/provide some detail?	Complaints consisted of • Internal complaints (about the product such as package and labelling) • Some customer complaints Overall rate of complaint is still very low but company consider the increase in 2019 due to wider reach/use of product and resulting increase in production.
		Could the company comment on the nature of complaints? Do they relate to the same issue?	Most related to packaging, contents of package/kits Not related to the use of endo-sponge clinically
		Could the company comment on whether complaints are impacted by whether users undergo hands on training or not?	Not considered an issue

Appendix B: File attachments/additional information from question 5

Cedar
Healthcare Technology Research Centre

Questions for NICE Expert Advisers

Topic	Endo-SPONGE for treating colorectal anastomotic leakage (MT461)
Date sent	17 January 2020
Please respond by	5.00 pm (UTC/GMT) on Friday 24th January

Cedar has been commissioned by the National Institute for Health and Care Excellence (NICE) to carry out external assessments of clinical and economic evidence on behalf of the Medical Technologies Evaluation Programme.

The purpose of this document is:

- to facilitate researchers' understanding of the clinical topic
- to clarify technical information about a device, procedure, intervention or standard care comparator
- to check whether assumptions made in the literature or economic model reflect "real world" context and practices (with particular emphasis on the UK NHS).

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Instructions:
Please complete the final column of the following table with your response to each question.
The completed form should be returned by **5.00 pm (UTC/GMT) on Friday 24th January.**
In the subject line, please write "MT461 Endo-SPONGE: Expert responses".

No.	EAC Question	Expert Adviser response
Clinical Pathway		
1	What is the pathway of care for a patient with anastomotic leak?	Large anastomotic leak with significant par anal discharge or chronic low grade pelvic sepsis provided no contraindications such as Crohns fistula
2	Would you typically treat patients in an inpatient or outpatient setting or a combination of both?	Both
3	Do you consider vacuum assisted therapy (specifically endo-sponge) to be an operative or non-operative procedure	Non-operative procedure
4	Do you anticipate that Endo-SPONGE would replace current treatments or be an addition to current treatment options?	Not replace but be a very good alternative or in addition
5	For patients with anastomotic leak, would there be multiple attempts at conservative management using different treatment options before turning to surgical options?	Yes. Endo-sponge is labour intensive for both surgeon and patient. Even then, the concept is much safer and better for patients compared with major surgery
6	Could you provide an estimate of the number of patients in the UK who • Undergo low anterior resection/anastomosis • Experience anastomotic leak following surgery • Persistent leak following treatment (e.g. suture repair, fibrin glue, Endo-Sponge etc)	I do not know how many patients undergo anterior resection. Risk of leak in low anastomosis is circa 10-12%. Persistent leak following treatment over is rare given most leaks are not large cavity
7	Would antibiotics be given alone or in combination with other treatments?	It needs to be in combination
Pain Relief		
8	In your experience do patients require some form of pain relief before endo-sponge can be placed?	Yes
9	Would patients treated typically receive • Mild pain relief (gas&air) • General anaesthetic	Depends, I have experienced both depends on pain threshold and how deep the cavity is.
10	Would many patients (if any) receive mild pain relief and be proceed to general anaesthesia?	About half and half

No.	EAC Question	Expert Adviser response
11	How does this compare with other forms of treatment for anastomotic leak?	Fibrin glue does not really work. Suture is not applicable unless re-laparoscoped
Clinical Experience		
12	Did you encounter any problems while using Endo-SPONGE in practice?	Yes, labour intensive. We all have to be around for it. Not the best for patients in terms of attendance
13	What is the furthest segment of the intestines that can be reached and treated with EndoSPONGE?	8cm from verge
14	Following the removal of Endo-SPONGE and during an endoscopic exploration of the cavity, is perforation likely to occur? Are there any adverse events associated with repeated endoscopic explorations?	It's a sinus by then so perforation is unlikely to occur. I am not aware of issues with repeated endoscopic explorations.
15	Are you aware of any high-quality published evidence or any ongoing studies specifically relating to Endo-sponge, other than: • Popivanov (2019) • Shalaby (2019) **If yes, please provide the full reference(s).**	No
16	What are the most important potential study confounders to account for when assessing the effectiveness of vacuum-assisted therapy for anastomotic leak?	Width and depth of cavity. If small already then healing may have occurred as quick without Endosponge
17	Are there any other important issues directly related to this assessment which you would like to bring to the attention of Cedar/NICE?	Mindful of contraindications of its usage

Thank you very much for providing your expert input into this assessment.
All responses will be taken into consideration.

Cedar
Healthcare Technology Research Centre

Questions for NICE Expert Advisers

Topic	Endo-SPONGE for treating colorectal anastomotic leakage (MT461)
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No.	EAC Question	Expert Adviser response
Clinical Pathway		
1	What is the pathway of care for a patient with anastomotic leak?	Once the index of suspicion has been raised they require admission, IV fluids and IV antibiotics. Then investigation by CT with IV and preferably rectal contrast. Once confirmed the patient requires either drainage via IR or theatre and a defunctioning ileostomy if they do not have one already.
2	Would you typically treat patients in an inpatient or outpatient setting or a combination of both?	Inpatient setting
3	Do you consider vacuum assisted therapy (specifically endo-sponge) to be an operative or non-operative procedure	Non-operative procedure
4	Do you anticipate that Endo-SPONGE would replace current treatments or be an addition to current treatment options?	Addition
5	For patients with anastomotic leak, would there be multiple attempts at conservative management using different treatment options before turning to surgical options?	No
6	Could you provide an estimate of the number of patients in the UK who • Undergo low anterior resection/anastomosis • Experience anastomotic leak following surgery • Persistent leak following treatment (e.g. suture repair, fibrin glue, Endo-Sponge etc)	Reviewing the recent NBOCA annual report approximately 2760 patients have an anterior resection in Wales and England. The quoted leak rate is variable from 4-10%. Therefore the number experiencing a leak could range from 110 to 276 It is difficult to quantify the persistent leak rate, but a third of patients do not have their ileostomy reversed. One reason being a persistent leak, although there are concerns such as function.
7	Would antibiotics be given alone or in combination with other treatments?	In combination
Pain Relief		

No.	EAC Question	Expert Adviser response
8	In your experience do patients require some form of pain relief before endo-sponge can be placed?	I have no direct experience with sndo-sponge, but would imagine the first few changes would require a sedative such as midazolam or possibly a GA for the first procedure.
9	Would patients treated typically receive • Mild pain relief (gas&air) • General anaesthetic	Probably a GA for the first insertion, then midazolam thereafter for changes
10	Would many patients (if any) receive mild pain relief and be proceed to general anaesthesia?	See above
11	How does this compare with other forms of treatment for anastomotic leak?	This is a new technique, an addition to the armoury
Clinical Experience		
12	Did you encounter any problems while using Endo-SPONGE in practice?	I have no direct experience
13	What is the furthest segment of the intestines that can be reached and treated with EndoSPONGE?	I would expect it to be only used for low rectal anastomotic leaks in colorectal surgery
14	Following the removal of Endo-SPONGE and during an endoscopic exploration of the cavity, is perforation likely to occur? Are there any adverse events associated with repeated endoscopic explorations?	Unlikely due to the fibrosis, but always a possibilty
15	Are you aware of any high-quality published evidence or any ongoing studies specifically relating to Endo-sponge, other than: • Popivanov (2019) • Shalaby (2019) **If yes, please provide the full reference(s).**	No
16	What are the most important potential study confounders to account for when assessing the effectiveness of vacuum-assisted therapy for anastomotic leak?	Patient variability, patient factors vary widely and given the low numbers of leaks in a single institution creating a study design that mitigates these confounding variables would be tricky.

No.	EAC Question	Expert Adviser response
17	Are there any other important issues directly related to this assessment which you would like to bring to the attention of Cedar/NICE?	I have no clinical experience of using endo-sponge.

Thank you very much for providing your expert input into this assessment.
All responses will be taken into consideration.

Cedar
Healthcare Technology Research Centre

Questions for NICE Expert Advisers

Topic	Endo-SPONGE for treating colorectal anastomotic leakage (MT461)
Date sent	17 January 2020
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In the subject line, please write "MT461 Endo-SPONGE: Expert responses".

PLEASE SEE TEXT BELOW FOR ANSWERS

No.	EAC Question	Expert Adviser response
Clinical Pathway		
1	What is the pathway of care for a patient with anastomotic leak?	
2	Would you typically treat patients in an inpatient or outpatient setting or a combination of both?	
3	Do you consider vacuum assisted therapy (specifically endo-sponge) to be an operative or non-operative procedure	
4	Do you anticipate that Endo-SPONGE would replace current treatments or be an addition to current treatment options?	
5	For patients with anastomotic leak, would there be multiple attempts at conservative management using different treatment options before turning to surgical options?	
6	Could you provide an estimate of the number of patients in the UK who • Undergo low anterior resection/anastomosis • Experience anastomotic leak following surgery • Persistent leak following treatment (e.g. suture repair, fibrin glue, Endo-Sponge etc)	
7	Would antibiotics be given alone or in combination with other treatments?	
Pain Relief		
8	In your experience do patients require some form of pain relief before endo-sponge can be placed?	
9	Would patients treated typically receive • Mild pain relief (gas&air) • General anaesthetic	
10	Would many patients (if any) receive mild pain relief and be proceed to general anaesthesia?	

No.	EAC Question	Expert Adviser response
11	How does this compare with other forms of treatment for anastomotic leak?	
Clinical Experience		
12	Did you encounter any problems while using Endo-SPONGE in practice?	
13	What is the furthest segment of the intestines that can be reached and treated with EndoSPONGE?	
14	Following the removal of Endo-SPONGE and during an endoscopic exploration of the cavity, is perforation likely to occur? Are there any adverse events associated with repeated endoscopic explorations?	
15	Are you aware of any high-quality published evidence or any ongoing studies specifically relating to Endo-sponge, other than: • Popivanov (2019) • Shalaby (2019) **If yes, please provide the full reference(s).**	
16	What are the most important potential study confounders to account for when assessing the effectiveness of vacuum-assisted therapy for anastomotic leak?	
17	Are there any other important issues directly related to this assessment which you would like to bring to the attention of Cedar/NICE?	

Thank you very much for providing your expert input into this assessment.
All responses will be taken into consideration.

1. **What is the pathway of care for a patient with anastomotic leak?**

(Refer to Issues in professional practice, prevention, diagnosis and management of colorectal anastomotic leakage March 2016, ACPGBI)

Diagnosis of leakage

1. Clinician suspicion
2. Clinical evidence of sepsis, non-progression after surgery and or peritonitis
3. Raised serum markers of inflammation and sepsis
4. Radiological investigations
5. Treatment
    a. Sepsis 6
    b. Organ support if required
    c. Source control
        i. Conservative
        ii. Radiological drainage
        iii. EndoSPONGE
        iv. Laparoscopy/Laparotomy
        v. Diversion stoma or resect anastomosis and end stoma

2. **Would you typically treat patients in an inpatient or outpatient setting or a combination of both?**

Most patients are in sepsis which will require inpatient care.

In the context of role of EndoSPONGE, this could be initiated as an inpatient and may be followed up as an outpatient.

3. **Do you consider vacuum assisted therapy (specifically endo-sponge) to be an operative or non-operative procedure**

Any invasive procedure could be considered as an operative procedure from the patient perspective.

I would class it is as 'minimally' invasive as the cavity are accessible transanally quiet often and the EndoSPONGE can be deployed in my experience either without any adjuncts or with minimal pain killers. In one case we required sedation.

4. **Do you anticipate that Endo-SPONGE would replace current treatments or be an addition to current treatment options?**

Endosponge will remain an adjunct as it is a subgroup of colorectal anastomotic leakages (see later for more details).

I have recently read that it is considered for use in oesophageal leakage, which I do not have any first-hand knowledge.

5. **For patients with anastomotic leak, would there be multiple attempts at conservative management using different treatment options before turning to surgical options?**

It is not desirable to have prolonged attempt to manage an anastomotic leakages conservatively as there is usually underlying sepsis which precludes such an option. In the context of EndoSPONGE, it is important that the sepsis is controlled before the patient can be expected to be maintained on this device. If the sepsis is not controlled with the EndoSPONGE alone, it may require an operative intervention including proximal diversion of bowel which the managing surgeon has to consider.

6. **Could you provide an estimate of the number of patients in the UK who**
    a. Undergo low anterior resection/anastomosis

As per latest NBOCAP data, there were 4516 resections for rectal cancer in the year 2016-17

    b. Experience anastomotic leak following surgery

Reported leakage rate of around 11% after rectal surgery in systematic review

(Ann Surg. 2010 May;251(5):807-18. doi: 10.1097/SLA.0b013e3181dae4ed.Postoperative complications following surgery for rectal cancer)(Paun BC[1], Cassie S, MacLean AR, Dixon E, Buie WD. http://dx.doi.org/10.1136/gutjnl-2015-309861.786)

    c. Persistent leak following treatment (e.g. suture repair, fibrin glue, Endo-Sponge etc)

I apologise for not able to get a data for this. I do not have experience with suture repair or fibrin glue.

7. **Would antibiotics be given alone or in combination with other treatments?**

Antibiotic alone may not be adequate as more than often it will require source control.

8. **In your experience do patients require some form of pain relief before endo-sponge can be placed?**

Explained below

9. **Would patients treated typically receive**
    a. Mild pain relief (gas&air)
    b. general anaesthetic

The first placement of EndoSPONGE will require a General anaesthetic assessment of cavity deep in the pelvis by an experience surgeon and the suitability for placement of EndoSponge placement.

Subsequent placements/changes, as I mentioned previously, there were occasions where I have changed without any adjuncts in well-conditioned patients who is independent as an outpatient. In other occasions, I required sedation with the help of an anaesthetist for each change. It depends very much on the patient's tolerance and how close it is to the index operation.

10. Would many patients (if any) receive mild pain relief and be proceed to general anaesthesia?

Not in my experience as it will depend on the judgement made by the surgeon. After explaining to the patient what it entails, depending on the height of the cavity from the anal opening, patients tolerance and difficulty of endoscopic access an appropriate decision has to be made by the surgeon.

11. How does this compare with other forms of treatment for anastomotic leak?

As I mentioned previously, Endosponge is ideal for a subgroup of patients who had a low colorectal anastomotic leakage with an extra-peritoneal collection.

This low extraperitoneal anastomosis is usually protected by a proximal diversion ileostomy at primary surgery, which is a common practise by most colorectal surgeons considering the higher risk of anastomotic leakage in such cases.

In case of leakage, the proximal ileostomy tends to be protective and reduce the contamination (also dependent on prior bowel preparation preoperatively). However the local pus and leakage may still require source control.

We follow this algorithm as in the ACPGBI guidance referenced before.

In this algorithm pg 22 the case scenario 1, 2a and 2b could be managed using Endosponge instead of the Interventional radiology transperineal/ transanal drainage. Endosponge in these situations give a much better control over the effluent, ease of deployment and more efficient considering the larger calibre of draining tubes as against the small calibre of radiological drains.

12. Did you encounter any problems while using Endo-SPONGE in practice?

There is a very short and steep learning curve with the equipment. I had one occasion where a small ring from the neck of the lubricating gel was accidentally introduced into the cavity.

This was not identified until surgery was performed for completion resection of rectal stump.

I have raised it with the MHRA and the company, B Braun. To my understanding the company has since changed the design of the gel tube without the free plastic ring at the neck.

13. What is the furthest segment of the intestines that can be reached and treated with EndoSPONGE?

As mentioned above, this is clinically useful tool for extraperitoneal low colorectal anastomotic leakage.

To my understanding, EndoSPONGE is designed to be in the peritoneal cavity for drainage of any further proximal anastomosis. From my clinical experience I will not suggest its use for any proximal leakages.

This is because the access transanally by open or endoscopic method will be difficult. Higher anastomotic leakage will also be open to the peritoneal cavity with associated extensive contamination, requiring laparotomy.

I am aware EndoSPONGE is now been trialled with results for Oesophageal anastomotic leakage. However, I do not have experience with this to give any further comments.

14. **Following the removal of Endo-SPONGE and during an endoscopic exploration of the cavity, is perforation likely to occur? Are there any adverse events associated with repeated endoscopic explorations**

The endosponge is introduced into the cavity of collection through a perforation in the bowel (ie, the dehiscence of anastomosis). The aim of the treatment with the Endosponge is also to maintain the perforation until the cavity heals completely following which the perforation is allowed to heal over.

I haven't had any adverse impact from the repeated procedure. The mental health of the patient through the process is important as it can be prolonged and repeated visits to the hospital may be required.

In one case, the anaesthetist raised the risk of neurological impact in older individuals who have repeated GA. We changed to sedation which worked well as short GA.

15. **Are you aware of any high-quality published evidence or any ongoing studies specifically relating to Endo-sponge, other than:**

- Popivanov (2019)
- Shalaby (2019)

If yes, please provide the full reference(s).

None I could reference, however I cannot claim to have done an extensive search from time constraints.

16. **What are the most important potential study confounders to account for when assessing the effectiveness of vacuum-assisted therapy for anastomotic leak**?

If a study has to be set up to study this, the most important factors to consider will be

a. The lack of uniformity of intervention among surgeons for anastomotic leakage
b. The lack of clear radiological criteria for extraperitoneal leakage
c. Lack of knowledge of Endosponge among surgeons
d. No clear clinical criteria for the 2 different settings on the EndoSPONGE suction bottle
e. Differing pain control requirements of patients requiring different setups.
f. Different healing rates of cavity dependent on patient's co morbidity.

g. Difficulty in referencing the size of the sponge introduced as they require trimming as the cavity gets smaller.

17. Are there any other important issues directly related to this assessment which you would like to bring to the attention of Cedar/NICE?

I do not have any concerns except that the table form do not give enough space for description and very short time line initially provided.

Appendix C: File attachments/additional information from question 6

Telephone Call with clinical expert (17/02/2020), notes have been verified by clinical expert.

Query	Comment
Can you provide some oversight on the clinical pathway and where Endo-SPONGE is likely to fit?	Endo-SPONGE is not a replacement, it is an additional treatment option. The decision to use endo-SPONGE will be based on a number of factors including patient condition, location and size of leak, why the leak occurred. Left for the clinical judgment. Most of these patients have already had a de-functioning stoma Intervention (with Endo-SPONGE or other) may not be required. Treatment involves management of initial sepsis symptoms and once patient is stable, further treatment may be considered (e.g. Endo-SPONGE)
Are there any contra-indications	Yes J pouch (IPAA) Low coloanal anastomosis generally although might be possible in some cases
Is there a particular grading system for AL that is used in the UK?	I'm not that familiar. It's a guide, very much dependent on patient's situation.
Can you comment on the use of the terms acute/chronic leak in relation to endo-sponge?	I wouldn't use endo-sponge immediately. I'm unsure what's meant by acute/chronic in this context. Clinical (as opposed to subclinical AL) AL not a common but significant problem and consider how bothersome clinically to a patient before treating
Would the majority of patients having colorectal surgery be for colorectal cancer?	Yes, likely to be mostly rectal cancer patients but there will be other indications, especially in teaching centres where it will be done for other conditions. E.g. endometriosis, mesh erosions from rectopexy etc
Can you comment on the long term survival of the patient group (patients undergoing colorectal surgery) regardless of whether they have an anastomotic leak or not?	Patients with AL are likely to have lower survival than patients with no AL. Ann Surg. 2011 May;253(5):890-9. **Increased local recurrence and reduced survival from colorectal cancer following anastomotic leak: systematic review and meta-analysis. Having said that, a paper this year (level 3) suggested the contrary.** Dis Colon Rectum. 2019 Mar;62(3):286-293. **Influence of Anastomotic Leak After Elective Colorectal Cancer Resection on Survival and Local Recurrence: A Propensity Score Analysis. As I said on the phone, one needs to view the 2011 paper with care given the heterogeneity of the study**
Could you comment on the length of time is takes to apply Endo-SPONGE. Literature suggests 15 minutes	15 minutes just to apply Endo-SPONGE seems reasonable however there are a number of other factors which need to be considered when determining the full time it takes to complete an appointment such as need for anaesthetic (GA or local), theatre time. Organising the procedure takes a lot of work. These are not emergency patients so they go to the bottom of the list. Total time could easily be 2 hours but this may include time making arrangements. For the ones needing sedation or GA, a district hospital under

	emergency pressures can take hours for the patient hanging around in recovery. I would not underestimate the 2 hours.In my very few experience, a range of 30 mins and 1 hour from entering to leaving theatre would not be too inaccurate. Patient needing to go to theatre has added time of sending, WHO checklist, sedation or GA time, washout if indicated etc so there is always additional time. Not all go to theatre and then it could be quicker. I've never done this as an outpatient procedure.
Can you comment on the staff that may be required for an Endo-SPONGE application?	In my experience (primarily inpatients) Consultants or registrars to apply Endo-SPONGE Anaesthetist if GA or sedation (not always with sedation) is required Other members of clinical team to arrange treatment/theatre etc.
Can you comment on any additional length of stay associated with Endo-SPONGE?	No, my patients are already inpatients. No obvious additional length of stay with Endo-SPONGE The use of endosponge means that the patient is in hospital longer with such symptomatic leak
Can you clarify the difference between stoma/ileostomy reversal and restoration of bowel continuity?	Protective stoma is given as the risk of AL is higher in low colorectal anastomosis than high anastomosis unless there are additional risk factors for a leak such as patients on immunosuppressants etc. Stoma/ileostomy reversal is done with the intention of restoring bowel continuity. I would consider these to be indicative of the same thing.

Appendix D: File attachments/additional information from question 7

The notes from this call have been sent to the clinical expert for verification but we have not had a response as of 10/03/2020

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1. Is there a standard grading system in use in the UK for grading anastomotic leaks?

Yes, but this is largely used for presentations/publications etc. In clinical terms, a patients either has a leak or doesn't.

2. Could you provide some clinical insight into the difference between a chronic and acute leak (we have seen literature referring to this but no clear definition)

An acute leak is generally one diagnosed in the first few days post-surgery. A chronic leak however is a leak that is likely to have occurred in the first few days post-surgery but did not get picked up until later. Generally hasn't healed because the patient has been defunctioned during primary surgery.

3. Are there any specific contraindications for Endo-SPONGE treatment

Use for low or rectal anastomosis

Patients with IAAP not contraindicated

Largely dependent on patient condition and location of anastomotic leak

4. Is the primary indication for colorectal surgery colorectal cancer or would the patient group comprise a number of different indications for surgery?

70-75% of patients will be having primary surgery for rectal cancer.

5. Without an anastomotic leak, what would the expected/anticipated survival rate for a group of patients undergoing colorectal surgery be? (If it is predominantly colorectal patients, what would 5 and 10 year survival be)

Approximately 65% (5 year survival) – a 10 year time horizon in the model would be appropriate.

6. In your experience, does treatment with Endo-SPONGE result in a change in length of hospital stay (increased/decreased) compared with other options for managing leak?

Not necessarily, patients are likely to already be in hospital when their leak is diagnosed so managing and treating the leak will not necessarily add any extra length to their stay. It may be that endo-SPONGE treatment can continue treatment in an outpatient setting.

7. Literature suggests that Endo-SPONGE application takes approximately 15 minutes however we are concerned this does not reflect the totality of treatment time for a patient. In your experience;
    a. is 15 minutes a reasonable estimate for application of Endo-SPONGE

Yes, 15 minutes to apply Endo-SPONGE seems sensible.

    b. approximately how long would the total treatment time take for a patient requiring theatre (inpatient, general anaesthetic)

Depends on what the patient requires and when the Endo-SPONGE treatment happens. On diagnosis of anastomotic leak most patients will have a laparoscopy and ileostomy (defunctioning) and it would be feasible to do the first Endo-SPONGE treatment at this time. In this case, Endo-SPONGE treatment would only add an extra few minutes to the process.

    c. approximately how long with total treatment time take in the outpatient setting?

In an outpatient setting, Endo-SPONGE applications/changes would take approximately 20-25 mins.

8. What staff would be involved in an appointment/treatment with Endo-SPONGE?

Consultant (surgeon who performed the primary surgery).

9. In your experience, what proportion of patients need a GA?

Usually the first placement however this may not be an additional general anaesthetic if the Endo-SPONGE application is being done as part of the leak diagnosis and management.

10. Is there a standard definition for what qualifies as an early leak (we have seen some literature suggesting 60 days post op).

Early versus late leak is related to when the leak is diagnosed by the clinical team rather than when the leak actually occurs as most leaks will have occurred quite soon following initial surgery but just not been picked up.

11. Would most patients have a protective stoma following a leak diagnosis
    All patients will have a protective stoma if they haven't already had one as part of primary surgery.

    General Comments
    Overall, Endo-SPONGE would not replace anything in the current clinical pathway. It would be an adjunct to current treatment options including antibiotics and percutaneous abdominal drainage.
    In general patients with leak will go back to theatre for laparoscopy, drain insertion to drain the abscess, defunctioning stoma and washout of the area. During this procedure it may be appropriate to begin Endo-SPONGE treatment as well.
    - ***Antibiotics will be given to all patients with a leak as they will have symptoms (infection, sepsis) to manage/prevent so antibiotics would not be an appropriate comparator to Endo-SPONGE.***
    - ***Percutaneous drainage would not be an appropriate comparator as all patients with leak will have drains inserted and Endo-SPONGE would be an add-on.***

    The main benefit with Endo-SPONGE is likely to be in the fact that is can reduce the amount of time a patient will have a stoma by a significant amount of time compared with not using Endo-SPONGE (can reduce the time to stoma reversal by weeks or months) this will

    - ***Improve patient quality of life***
    - ***reduce the costs associated with stoma management/stoma care***

Appendix E: File attachments/additional information from question 8

Cedar

Healthcare Technology Research Centre

Please note:

The content of email correspondence (and associated attachments) is recorded in a table to ensure that all information relevant to the assessment of the topic is captured. The table is shared with the NICE Medical Technologies Advisory Committee (MTAC) as part of the committee documentation, and is published on the NICE website at public consultation

1. Is there a standard grading system in use in the UK for grading anastomotic leaks?

As per the ACPGBI document, it can be classed as intra peritoneal leakage and extra-peritoneal leakage broadly. Also there is a classification of severity of intra-peritoneal leakage in the same document (Page 22-23, Prevention, diagnosis and management of colorectal anastomotic leakage, March 2016).

The endosponge is ideal for extra-peritoneal leakage of a low colorectal anastomosis, with level 2 or 3 severity), for the reason that the patient has localised sepsis in the pelvis.

2. Could you provide some clinical insight into the difference between a chronic and acute leak (we have seen literature referring to this but no clear definition)

Chronic sinuses from the anastomosis tend to be radiological finding and usually does not present clinically as acute sepsis. Endo Sponge is not suitable for those scenarios.

3. Are there any specific contraindications for Endo-SPONGE treatment

Absolute CI will be allergy to the material used.

Relative CI would be the following:

a. site of the anastomotic leakage: it is not suitable for intraperitoneal perforation of colonic anastomosis with or without sepsis. It is ideal for a extraperitoneal colorectal anastomosis with localised sepsis.
b. If the patient has grade 4 or 5 sepsis, it may require a laparotomy and resection of anastomosis, than a endosponge alone.
c. Lack of proximal diversion, as in a de-functioning proximal stoma, is detrimental in its success.
d. Patient factors including mental health as this will require repeated procedures.

4. Is the primary indication for colorectal surgery colorectal cancer or would the patient group comprise a number of different indications for surgery?

Surgery resulting in a low colorectal anastomosis (in the context of Endo Sponge) can be varied. However, on a national context, the commonest indication for an operation with a low anastomosis will invariably be colorectal cancer.

Other indications will include Ulcerative colitis, where following total colon resection and a pouch could be formed from small bowel and anastomosed to low rectum. Other rarer possibilities are for resection of large polyps in rectum and surgery for rectal trauma.

5. Without an anastomotic leak, what would the expected/anticipated survival rate for a group of patients undergoing colorectal surgery be? (If it is predominantly colorectal patients, what would 5 and 10 year survival be)

There is extensive data regarding this particular question about risk of local recurrence and long term survival after an anastomotic leakage in colorectal cancer resection.

The guidance from ASGBI had clearly stated that there is a higher risk of local recurrence, and reduction in the overall survival and disease free survival and this is the general opinion held in colorectal discussions and meetings (pg 11, Issues in clinical practice, Prevention, diagnosis and management of Colorectal anastomotic leakage, March 2016).There are studies which has shown no significant impact following rectal surgery in particular, however these are isolated reports and to my knowledge not the accepted wisdom.

As regarding Endo Sponge, it may be difficult to compare a cohort of patients who had Endo Sponge treatment for anastomotic leakage versus none. Moreover, the risk is the leakage itself in my opinion, than the treatment they may receive for leakage.

6. In your experience, does treatment with Endo-SPONGE result in a change in length of hospital stay (increased/decreased) compared with other options for managing leak?

In my opinion, Endo-Sponge gives better control of the site of leakage which reduces the requirement for major surgical intervention, reduce impact of sepsis by giving source control in appropriate cases and thus reduce hospital stay overall. In these patients, they will be able to leave in-patient care much earlier as was the case with the 3 of my patients and be managed as outpatients with Endo-Sponge. This made a significant reduction in morbidity and improvement in their mental health.

7. Literature suggests that Endo-SPONGE application takes approximately 15 minutes however we are concerned this does not reflect the totality of treatment time for a patient. In your experience;

I assume that this is regarding patients who already had an Endo-Sponge placed and requiring change.

    a. is 15 minutes a reasonable estimate for application of Endo-SPONGE

The actual procedure to change an Endo-sponge may take only 15 minutes, however there are logistics involved in setting up, including endoscopy, sedation or even in OPD. So I agree it is an underestimate of the actual time it may be required.

The analogy will be with an inguinal hernia operation in theatre, where the operation itself may take 45minutes, but the bringing the patient to theatre, anaesthetising, check list, operation itself and waking them up and out of theatre will all together take up to 60-75 minutes!

b. approximately how long would the total treatment time take for a patient requiring theatre (inpatient, general anaesthetic)

If under GA (or deep sedation) as in one of my patients, the anaesthetic time to find an IV access and then to sedate them will take up to 15minutes anaesthetic time in my recall.
In outpatient settings, it will be upto 15 min to set up the required equipment, position patient on left lateral, analgesic administration if required and proceed to change an Endo-Sponge.
I have not had a patient who required change by endoscopy, hence cannot comment of the time required with this setup.

c. Approximately how long with total treatment time take in the outpatient setting?

As above

In my opinion, it is not appropriate to compare procedure depending on time it may take. I have patients who need reassuring and discussion before we proceed.

I believe we should be comparing the ease of procedure, reproducibility of efficacy by different teams and how the patients cope.

8. What staff would be involved in an appointment/treatment with Endo-SPONGE?

Again, I assume we are discussing patients who had an Endo-Sponge placed already by a Colorectal Consultant and requiring change.

In majority of the episodes, as a Colorectal Consultant, I was directly involved in the procedure.

I had Higher Surgcial trainees who were able to change them under guidance.

I also have a Surgical care practitioner (SCP) who has changed them very effectively even in my absence.

It is a reflection of the ease with which it can be placed once the patient and the operator knows the routine. However, it will require experience and the confidence form the patient to get to that place and also will require the guidance of a colorectal Consultant to assess the progression of healing.

In short it has to be Consultant delivered or led at all times.

9. In your experience, what proportion of patients need a GA?

One of the 3 patients had GA initially and then we changed to deep sedation for changes. The other 2 were managed without GA or sedation in OPD, for changes of Endo-Sponge.

Please note that the initial assessment and decision of placement required GA for all 3 of my patients.

10. You mention in you initial information that the time from index operation would have an impact on need for GA. Would patients who have a leak sooner be more likely to need GA?

    Although, I do not remember making that statement, as mentioned above, all 3 of my patients required GA for assessment of the cavity and decision on Endo-Sponge management initially.

    The patient, who required a GA initially for further changes, had a more extensive sepsis of her perineum involving a rectovaginal fistula. She then settled to have sedation to have them changed. I can only extrapolate from the limited number of cases, that if the sepsis is significant, the patients are likely to need GA.

11. Is there a standard definition for what qualifies as an early leak (we have seen some literature suggesting 60 days post op).

All cases which are likely to be managed in a hospital with Endo-Sponge are acute conditions with leakage from colorectal anastomosis with associated sepsis. Endo-Sponge is a form of source control for such situations.

In leaks picked up by radiological investigations with none or minimal symptoms to the patient, will not warrant management with Endo-Sponge. In my experience they are managed by conservative measures (watch and wait).

NICE National Institute for Health and Care Excellence

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

External Assessment Centre Report factual check

Endo-SPONGE for treating colorectal anastomotic leak

Please find enclosed the assessment report prepared for this assessment by the External Assessment Centre (EAC).

You are asked to check the assessment report from CEDAR to ensure there are no factual inaccuracies contained within it. If you do identify any factual inaccuracies you must inform NICE by 12pm, **16th March 2020** using the below proforma comments table. All your comments on factual inaccuracies will receive a response from the EAC and when appropriate, will be amended in the EAC report. This table, including EAC responses will be presented to the Medical Technologies Advisory Committee and will subsequently be published on the NICE website with the Assessment report.

11th March 2020

Issue 1

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 9 section 3.1 “The EAC also noticed an error in spelling in the company literature search which may have impacted the search findings although the EAC corrected this spelling error when running the searches and did not identify any major discrepancies.”	Request removal of this sentence	The EAC acknowledge a typing error in the documented literature search and the repeat search show minimal discrepancies – indicating the errors occurred in transfer of information into the submitted document rather than search itself	Thank you for your comment. The spelling error relates to ‘Company search strategy for Outcomes for Endo-SPONGE’ set 15 (see appendix A of assessment report), the EAC will keep the sentence as it demonstrates to external audiences that the error was noted and investigated.

Issue 2

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 11 Arezzo - Design and intervention “case series” EAC comments “retrospective”	Change “case series “ to “retrospective case series”	Alignment within columns of table	Thank you for your comment. The EAC have made this change

Issue 3

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 11 Arezzo -Participants and settings column	Addition of following to Participants and settings column: Median cavity length 4cm (range 2-9cm)	Currently missing information on cavity size. Severity of leak requested in the scope – cavity size is an indication of severity.	The EAC has made this amendment

Issue 4

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 11 Arezzo - EAC comments on “small case series”	Small case series, although over a long duration of 4.5 years – general limits of incidence of anastomotic leak occurrence.	Small sample size is a natural limitation of the occurrence rate of anastomotic leak being so low and not due to poor study design which was of long duration.	Thank you for your comment. The EAC understand that small sample sizes are a natural limitation however it is important that the small sample sizes of the studies are noted and as this is simply the data extraction tables, this is not the place in the Assessment Report to discuss this. The EAC has been very clear in the conclusions that the small study sample sizes are the result of the low rate of anastomotic leak and that larger sample sizes would not be achievable. The EAC has not made any change to this however it has been further highlighted in a new section ‘Key points for consideration’.

Issue 5

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 12 Boschetti - average size of cavity and distance from anal verge not included in participants and settings	Add the following to participants and settings: Mean size of fistula was 7±4.6cm range (2-20cm)	Currently missing information on cavity size and distance from anal verge, provided in the study. Severity of leak and distance from anal verge requested in the scope,	The EAC has made this amendment

	Mean level from anal verge 6.2±4.6cm (range 2-20cm)	cavity size is an indication of severity.	

Issue 6

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 12 Boschetti - male/female split and age not included in participants and settings	Add the following to participants and settings: 22 Males, 7 Females, mean age 68±10 years (range 51-88)	Male female split included in participants and settings for other studies, providing continuity through document and accurate patient description.	The EAC has made this amendment

Issue 7

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 12 Boschetti - participants and settings number of patients with neo adjuvant missing	19 patients treated with neoadjuvant radio-chemotherapy	Current description "23 with rectal cancer and neoadjuvant chemo-radiotherapy" implies all 23 patients were treated with neoadjuvant – radiotherapy	The EAC have made this amendment

Issue 8

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 12 Boschetti - participants and settings description of 3 sigmoiditis patients is misleading	3 sigmoiditis, 1 for left colonic cancer , 2 for right colonic cancer with peritoneal carcinosis treated by hyperthermic intraperitoneal	The study describes the details of the 3 sigmoiditis patients, current details in the table read like 3	The EAC have clarified this

	chemotherapy and left colectomy with colorectal anastomosis	sigmoiditis and then 3 separate patients described 1 with left colonic cancer and 2 with right colonic cancer.	

Issue 9

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 12 Boschetti - Outcomes, Currently "Unclear, the outcomes are not defined in the methods of the study but the results report"	Removal of sentence and addition of : Success rate, success defined as closed cavity (described as <1cm),	Methods describe that "during each procedure the sponge is cut to the size of cavity, which was measured with the endoscope"… "treatment was stopped when cavity length was close to 1cm"	Thank you for your comment. The study outcomes are not clearly defined, it should be specified what will be measured, nearest reporting standard is PROCESS which states in methods section of checklist: 4e 'measures taken prior to surgery' and 4j 'follow-up measures'

Issue 10

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 12 Boschetti - Outcomes, missing sustained long term closure/success	Addition of 'long term success.	Study describes secondary failures, provides insight into long term success.	As above

Issue 11

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 12 Boschetti - EAC comments on “small sample size”	Small sample size although over a long duration of 3 years – general limits of incidence of anastomotic leak occurrence.	Small sample size is a natural limitation of the occurrence rate of anastomotic leak being so low and not due to poor study design which was of long duration.	Thank you for your comment. The EAC understand that small sample sizes are a natural limitation however it is important that the small sample sizes of the studies are noted and as this is simply the data extraction tables, this is not the place in the Assessment Report to discuss this. The EAC has been very clear in the conclusions that the small study sample sizes are the result of the low rate of anastomotic leak and that larger sample sizes would not be achievable. The EAC has not made any change to this however it has been further highlighted in a new section ‘Key points for consideration’.

Issue 12

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 13 Huisman - Design and intervention currently says “Endo-SPONGE with surgical closure”	Change to “Endo-SPONGE, with surgical closure depending on surgeon preference”	Study describes “Depending on surgeon preference, transanal closure of the defect was performed after a short period of endo-SPONGE therapy” indicating that some, not all patients had transanal	The EAC has made this amendment

		closure. This is mentioned further down in design and intervention although the statement above indicates all patients have additional transanal closure and is misleading.	

Issue 13

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 13 Huisman - EAC comments "The study intervention was Endo-SPONGE followed by a planned surgical closure of defect"	Remove and replace with "some patients treated with Endo-SPONGE alone and others with Endo-SPONGE and transanal closure, depending n the preference of surgeon, patient groups not identifiable in study data.	Misleading – implies all patient were treated with closure in addition to Endo-SPONGE, methods describes "at preference of surgeon"	The EAC has made this amendment

Issue 14

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 13 Huisman - EAC comments on "small case series (high risk of bias)"	Small sample size although over a long duration of 5 years – general limits of incidence of anastomotic leak occurrence.	Small sample size is a natural limitation of the occurrence rate of anastomotic leak being so low and not due to poor study design which was of long duration.	Thank you for your comment. The EAC understand that small sample sizes are a natural limitation however it is important that the small sample sizes of the studies are noted and as this is simply the data extraction tables, this is not the place in the Assessment Report to discuss this. The EAC has been very clear in the conclusions that the small study sample sizes are the result of the low rate of anastomotic leak and that

			larger sample sizes would not be achievable. The EAC has not made any change to this however it has been further highlighted in a new section 'Key points for consideration'.

Issue 15

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 15 Jimenez-Rodriguez - Design and intervention currently says "Endo-SPONGE. Depending on size of cavity 2 or more were used with pressure of 375 mmHg, sponges were change every 3 – 5 days"	Change to: "Endo-SPONGE. Depending on size of cavity 2 or more were used. Initially pressure of 375 mmHg was used ad modified to 150 mm Hg at the first sponge replacement, sponges were change every 3 – 5 days.	Current description indicates 375 mm Hg was used for all occasions where 2 or more sponges were used, however methods describe using 375 mm HG for all initial sponges and reducing to 150 mm Hg once the first sponge is replaced.	The EAC has made this amendment

Issue 16

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 16 Katz - Design and Interventions – has results in the intervention section	Remove: Mean number of exchanges: 3.6 (range 3–5 exchanges) from design. Sepsis control was achieved following the initial treatment (antibiotics, Endo-SPONGE, and diversion).	These are results and not study design or intervention process	Thank you for your comment. These were already in the results table. The EAC has deleted them from the study design section.

Issue 17

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 16 Katz - Design and Interventions –missing irradiation therapy details	Add “None of the patients underwent irradiation prior to surgery.”	Missing pre surgical treatment information	The EAC has made this amendment

Issue 18

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 16 Katz - Design and Interventions. A diverting stoma was constructed in 2/3 patients who had no previous diversion	3/5 patients had a diverting stoma at initial surgery and 1 patient had a stoma created following leak	Data in text does not match the table	Thank you for your comment. The EAC agrees that the study table and text do not match. The EAC have left the numbers as those reported in the text but noted the discrepancy in the comments.

Issue 19

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 16 Katz - Participants information data missing	Addition of following: Median dehiscence 180 (degrees) range 50-270 degrees Median time to leak diagnosis 7 days (range 4-14 days).	Describes size of leak being treated, time to diagnosis and time to treatment. Severity of leak and time to leak diagnosis requested in the scope, cavity size is an indication of severity.	The EAC has made this amendment

	Median time to first sponge placement 13 days (range 9-33)		

Issue 20

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 17 Keskin - Design and intervention – outcome as intervention “Average number of sponge applications was 2.2 (range, 1 to 5).”	Remove from design and add “average number of sponge applications” to the outcome	To maintain consistency across the paper summaries in table 1	Thank you for your comment. These were already in the results table. The EAC has deleted them from the study design section

Issue 21

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 17 Keskin - Design and intervention “Endo-SPONGE. Applied under sedation by a surgeon”	Replace with “Endo-SPONGE applied under sedation in the endoscopy unit by a surgeon”	Omission of place of insertion, important in gaining data for where procedure takes place.	The EAC has made this amendment

Issue 22

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 17 Keskin – Participants and setting. “Hospital”	Remove “Hospital”	This is not consistent with (a) other summaries in table 1 and (b) patient were treated both and in patients and out patients, this indicates all	The EAC note that this information has been included for other studies so has not deleted this however has clarified

		patient were in patient and is misleading.	that the procedure was carried out in the endoscopy unit.

Issue 23

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 17 Keskin - Participants and setting, missing time to leakage identification.	Add “Eight leaks were identified early and 7 leaks identified late”	Time to anastomotic leak diagnosis requested in scope	The EAC has made this amendment

Issue 24

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 17 Keskin - Outcome, missing information	Add “lumen integrity, stoma closure rate, impact of early and late diagnosis on treatment success, any recurrent abscesses”	Detailed outcomes missing from results.	The EAC has made this amendment but clarified that these outcomes were not clearly stated in the methods/study design.

Issue 25

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 18 Kuehn - Design and intervention – sedation requirements	Addition of “EVT usually performed without the need for sedation or anaesthesia”	Use of sedation discussed in other summaries – this allows for consistency and sedation used may be important to the decision	The EAC has made this amendment

Issue 26

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 18 Kuehn - EAC comments, on “small sample size”	Small case series, although over a long duration of 8 years – general limits of incidence of anastomotic leak occurrence.	Small sample size is a natural limitation of the occurrence rate of anastomotic leak being so low and not due to poor study design which was of long duration.	Thank you for your comment. The EAC understand that small sample sizes are a natural limitation however it is important that the small sample sizes of the studies are noted and as this is simply the data extraction tables, this is not the place in the Assessment Report to discuss this. The EAC has been very clear in the conclusions that the small study sample sizes are the result of the low rate of anastomotic leak and that larger sample sizes would not be achievable. The EAC has not made any change to this however it has been further highlighted in a new section ‘Key points for consideration’.

Issue 27

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 19 Manta - design and interventions, “no comparator”	Add as a minimum “ over the scope clips, over the scope clips with self expanding metal stent”	While there is no comparator to percutaneous drain there are comparators. For the same leaks as treated by Endo-SPONGE (Anterior rectal resections and left/right or total colectomy) there	Thank you for your comment. This study was not designed to compare outcomes of different treatments hence the EAC decision to include only the Endo-SPONGE data. The EAC has

		were comparators treated with over the scope clips, over the scope clips with self expanding metal stent.	added some details of the alternative treatments in response to the company comments and has included extra information to the table to clarify the situation.

Issue 28

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 19 Manta - Outcomes	Addition of "Length of stay"	While Endo-SPONGE treatment was an outpatient with 0 length of stay, the comparators for similar anastomotic leaks had variable length of stays greater than endo-SPONGE. Omission of this outcome is misleading.	Thank you for your comment. The EAC has amended the table to state that length of stay was an outcome for the whole study but not applicable to Endo-SPONGE as it was done in an outpatient setting. This information was already recorded in the results table later in the document but has been added here for further clarity.

Issue 29

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 19 Manta – Participants, N=7	N=29 lower Gastrointestinal leaks, N=7 treated with Endo-SPONGE, N=18 OTSC, N=4 OTSC and SEMS.	Indicates study is smaller than it is and omits the comparators involved.	The EAC has added information for clarity. See response to Issue 27 for details.

Issue 30

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 19 Manta - Comments, "lack of comparator"	Lack of standard treatment comparator	Currently mis-leading as the study covered other endoscopic treatments not just Endo-SPONGE, however accept that there is no standard treatment comparator involved	The EAC has added information for clarity. See response to Issue 27 for details.

Issue 31

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 19 Manta - EAC comments, Small case series (high risk of bias)	Small case series due to multiple endoscopic options available for treatment, although over a long duration of 5 years – general limits of incidence of anastomotic leak occurrence.	Small sample size is a natural limitation of the occurrence rate of anastomotic leak being so low and not due to poor study design which was of long duration and this study covered N=29 lower GI leaks, which is large in this field.	Thank you for your comment. The EAC understand that small sample sizes are a natural limitation however it is important that the small sample sizes of the studies are noted and as this is simply the data extraction tables, this is not the place in the Assessment Report to discuss this. The EAC has been very clear in the conclusions that the small study sample sizes are the result of the low rate of anastomotic leak and that larger sample sizes would not be achievable. The EAC has not made any change to this however it has been further

			highlighted in a new section 'Key points for consideration'.

Issue 32

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 20 Milito - Design and intervention, time to diagnosis of leak missing	Median time to diagnosis 14 days (range 7-21)	Time to diagnosis request as consideration in scope	The EAC has made this amendment

Issue 33

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 20 Milito - EAC comments, small number of patients	Small case series although over a long duration of 7 years – general limits of incidence of anastomotic leak occurrence.	Small sample size is a natural limitation of the occurrence rate of anastomotic leak being so low and not due to poor study design which was of long duration and this study	Thank you for your comment. The EAC understand that small sample sizes are a natural limitation however it is important that the small sample sizes of the studies are noted and as this is simply the data extraction tables, this is not the place in the Assessment Report to discuss this. The EAC has been very clear in the conclusions that the small study sample sizes are the result of the low rate of anastomotic leak and that larger sample sizes would not be achievable. The EAC has not made any change to this however it has been further

			highlighted in a new section 'Key points for consideration'.

Issue 34

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 22 Nerup – EAC comments	Small case series although over a long duration of 4 years – general limits of incidence of anastomotic leak occurrence.	Small sample size is a natural limitation of the occurrence rate of anastomotic leak being so low and not due to poor study design which was of long duration and this study	Thank you for your comment. The EAC understand that small sample sizes are a natural limitation however it is important that the small sample sizes of the studies are noted and as this is simply the data extraction tables, this is not the place in the Assessment Report to discuss this. The EAC has been very clear in the conclusions that the small study sample sizes are the result of the low rate of anastomotic leak and that larger sample sizes would not be achievable. The EAC has not made any change to this however it has been further highlighted in a new section 'Key points for consideration'.

Issue 35

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 23 Riss – EAC comments	Small case series although over a long duration of 3 years – general limits of incidence of anastomotic leak occurrence.	Small sample size is a natural limitation of the occurrence rate of anastomotic leak being so low and not due to poor study design which was of long duration and this study	Thank you for your comment. The EAC understand that small sample sizes are a natural limitation however it is important that the small sample sizes of the studies are noted and as this is simply the data extraction tables, this is not the place in the Assessment Report to discuss this. The EAC has been very clear in the conclusions that the small study sample sizes are the result of the low rate of anastomotic leak and that larger sample sizes would not be achievable. The EAC has not made any change to this however it has been further highlighted in a new section 'Key points for consideration'.

Issue 36

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 23 Riss - Participant and setting	Addition of "all n=9/9 had initial anterior resection due to low rectal cancer"	Consistency with previous summaries	The EAC has made this amendment

Issue 37

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 23 Riss - Participant and setting – leak onset time missing	Addition of “One patient showed an early anastomotic dehiscence 7 days after LAR. In all other patients (n = 8), the median time from primary surgery (LAR or Hartmann) to anastomotic leakage was 2.5 month (range: 1–24).”	Scope request data on time to leak onset	The EAC has made this amendment

Issue 38

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 27 Srinivasamurthy – Participants, time to leak detection	Add “ median time to leak detection 29 days (range 10-115) Remove “time to leakage detection” from outcome	Time to detection in the scope	The EAC has made this amendment

Issue 39

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 27 Srinivasamurthy – Outcomes, “ileostomy reversal”	Add “and time to stoma reversal”	Time to stoma reversal important to include.	The EAC has made this amendment

Issue 40

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 28 Strangio - Participant and setting – missing dehiscence size and cavity size	Add “Anastomotic leak extended from 70 to 270 degrees” “the median size of cavity was 56mm (range 15-100mm)”	Consistency between summaries and scope request details on size of leak dehiscence and cavity size fulfil this criteria.	The EAC has made this amendment

Issue 41

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 28 Strangio - Participant and setting – missing time to leak detection	Add “median time to leak detection 17 days (range 0-102 days)”	Time to leak detection required by the scope	The EAC has made this amendment

Issue 42

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 28 Strangio - EAC comments, “small case series”	Small case series although over a long duration of 5 years – general limits of incidence of anastomotic leak occurrence.	Small sample size is a natural limitation of the occurrence rate of anastomotic leak being so low and not due to poor study design which was of long duration and this study, n=25 is large for a frequency of 10% leak occurrence.	Thank you for your comment. The EAC understand that small sample sizes are a natural limitation however it is important that the small sample sizes of the studies are noted and as this is simply the data extraction tables, this is not the place in the Assessment Report

			to discuss this. The EAC has been very clear in the conclusions that the small study sample sizes are the result of the low rate of anastomotic leak and that larger sample sizes would not be achievable. The EAC has not made any change to this however it has been further highlighted in a new section 'Key points for consideration'.

Issue 43

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 29 Van Koperan - Participant and settings, "time to leak diagnosis missing"	The median duration between the initial surgery and the discovery of the leakage was 11 days (range 3–150 days).	Scope request time to leak detection and for continuity with other summaries	The EAC has made this amendment

Issue 44

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 29 van Koperan - Design and setting – missing number of patient with procedure performed without any sedation"	Add "seven patients underwent sponge placement without any anaesthesia"	Factual accuracy – omission is misleading	Thank you for your comment. The EAC considered that it was clear that the remaining 7 patients required no anaesthesia given the information provided. The EAC have amended this to include this detail.

Issue 45

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 30 Wasmann - Design – missing sedation details	Add “sponges were inserted and exchanged under light sedation”	Sedation requirements discussed in other summaries and provide details of procedure	The EAC has made this amendment

Issue 46

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 30 Wasmann - Design – Patient population – comparator number and patient details missing	Add “N=22 Patient treated with conventional management and N=18 treated with Endo-SPONGE and surgical closure” Add “(11 male, 11 female). Mean age at IPPA surgery was 34.68 (SD 12.98). Indication: 18/22 ulcerative colitis, 4/22 inflammatory bowel disease unclassified. ASA score 1 in 7/22, 2 in 14/22 and 3 in 1/22”	For clarity of comparator patient groups	The EAC has made this amendment

Issue 47

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 32 Weidenhagen - design and intervention, missing time to leak detection	Add “anastomotic leak was detected between the 3rd and 17th day post surgery, mean 8.2 SD 3.6 days”	Scope request time to leak detection and continuity with other summaries	The EAC has made this amendment

Issue 48

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 32 Weidenhagen - EAC comments, small number of patients	Small case series although over 2 years – general limits of incidence of anastomotic leak occurrence.	Small sample size is a natural limitation of the occurrence rate of anastomotic leak being so low and not due to poor study design which was of long duration and this study, n=29 is large for a frequency of 10% leak occurrence.	Thank you for your comment. The EAC understand that small sample sizes are a natural limitation however it is important that the small sample sizes of the studies are noted and as this is simply the data extraction tables, this is not the place in the Assessment Report to discuss this. The EAC has been very clear in the conclusions that the small study sample sizes are the result of the low rate of anastomotic leak and that larger sample sizes would not be achievable. The EAC has not made any change to this however it has been further highlighted in a new section 'Key points for consideration'.

Issue 49

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 33 Di Mitri – Outcomes/Design, missing procedure length	Add "procedure took on average 15 minutes"	Duration of procedure used in economic evaluation	The EAC has made this amendment

Issue 50

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 34 Martel CANNOT ACCESS FILE TO FACT CHECK			

Issue 51

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 38 section 4.1 paragraph 3. "All included studies had small sample sizes ranging from 3 participants (McAuley et al. 2013) to 34 participants (Weidenhagen et al. 2008)."	All included studies had small sample sizes ranging from 3 participants (McAuley et al. 2013) to 10 (Martel 2018) with the abstracts and from 6 (Katz 2016) to 34 participantants (Weidenhagen et al. 2008) within the full studies."	Details information split across the 3 abstracts compared with the 20 full studies	The EAC has made this change.

Issue 52

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 39 Section 4.2 Paragraph 1. "The company submission does not include a formal critical appraisal of the studies included in the clinical evidence review.	Propose remove or acknowledgment to comments below with addition of, "although the EAC acknowledge that there is no formal section within current NICE documentation requesting critical appraisal of the studies.	There is no specific section within the NICE submission document requesting critical appraisals of all studies. The company have now spotted a sub section in section 7 under Qualitative review stating	Thank you for your comment. The EAC have not made this amendment as they consider it is important to acknowledge that formal

There is no mention of the use of any checklist for appraising study quality."		"Explain why quantitative review is not appropriate and instead provide a qualitative review. This review should summarise the overall results of the individual studies with reference to their critical appraisal". As the majority of the company submission was meta-analysis this was unfortunately oversight.	critical appraisal of studies has not been conducted. This is not meant to be a criticism of the company process, simply a point to note for the clinical experts when reviewing the evidence.

Issue 53

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 39 Section 4.2 Paragraph 1. The company briefly highlights the limitations of Endo-SPONGE studies in section 5 of their submission. No details of how those limitations were assessed or their impact on the quality of the clinical evidence has been presented	Remove "No details of how those limitations were assessed or their impact on the quality of the clinical evidence has been presented"	Limitation were requested for each study in section 5, this was provided. Impact was not requested clearly in the submission form. The company shall take feedback from EAC on board for future work.	Thank you for your comment. The EAC have not made this amendment as they consider it is important to acknowledge that formal critical appraisal of studies has not been conducted. This is not meant to be a criticism of the company process, simply a point to note for the clinical experts when reviewing the evidence.

Issue 54

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 39 Section 4.2 Paragraph 1. The company has used results from these studies to make comparisons between effectiveness of Endo-SPONGE and other non-operative treatment options. There is no discussion in the company submission around how the studies were selected for inclusion or around the quality or limitations of these additional studies.	Remove “There is no discussion in the company submission around how the studies were selected for inclusion or around the quality or limitations of these additional studies.”	The company provided in Appendix B search performed along with inclusion and exclusion criteria. These studies were submitted to the same meta-analysis as the clinical evidence for Endo-SPONGE for quantitative review and as such were not requested for clinical appraisal within the submission document. The company acknowledge that is was difficult to fit the required information within the constraints of the submission tool. This information was provided to allow for a representation of the current conventional pathway and outcome - as the EAC acknowledge in their report that the pathway for AL treatment varies by patient and patient condition and as such without the generation of some information for the success of current conventional treatment no comparison could be made.	Thank you for your comment. The EAC has not made any amendments. The EAC acknowledge that the company have provided search strategies and the inclusion/exclusion criteria for those strategies however the company submission does not discuss the details of the studies included in the comparator evidence synthesis nor any decisions made on how relevant data from these studies has been selected. As a result, the EAC has not been able to validate much of the data. The EAC acknowledge that there are variations in the clinical pathway and agree that it is difficult to make comparisons between the Endo-SPONGE and current pathway studies however the EAC note that as data from the comparator evidence synthesis is used in the economic analysis, it is important that the potential limitations of these studies are clearly noted. This is not intended as a criticism of the company submission however the EAC consider it important to note that none of

			the studies in the comparator analysis have been critically appraised by either the company or the EAC.

Issue 55

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 41 Study characteristics paragraph 1. "stoma/ileostomy reversal and/or restoration of bowel continuity (11 studies),"	Change to "14 full studies"	14 full studies discuss success in stoma reversal/bowel continuity and to align with later text in document on page 45 and 46	Thank you for your comment. The EAC has made amendments to this section to ensure all numbers are consistent through the report.

Issue 56

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 41 Study characteristics paragraph 1. "complications (11 studies)"	Change to complications presence/absence (15 studies)	15 studies discuss presence or absence of complications, reporting of absence is equally important as reporting of presence of complications. Only reporting on the studies recording presence of complications is misleading	Thank you for your comment. The EAC has made the necessary amendments to include the studies reporting no complications.

Issue 57

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 41 Study characteristics paragraph 1. length of hospital stay (3 studies)	Change to “length of hospital stay (4 studies)”	Incorrect number reported	Thank you for your comment. The EAC has not made this change as length of stay is reported in 3 studies. Although Manta et al reported a length of stay, it was not for Endo-SPONGE as this was outpatient treatment. The EAC has therefore reported this the same way as for other studies with outpatient treatment.

Issue 58

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 41 Study characteristics paragraph 1. Omission of studies reporting ability for out-patient treatment	Addition of “Procedure performed as out-patient for some patients (7 studies)”	To balance LOS information ability to perform procedure with 0 day LOS offers balanced view as only 1 of the LOS papers covers use in out-patient setting. Important outcome to understand how procedure can be adopted.	Thank you for your comment. The EAC has not made any amendment here. The purpose of this section is to very briefly summarise what is reported in the papers. The EAC acknowledges and accepts the point from the company however in section 4.3, the section discussing length of stay does state that a length of stay outcome would not be applicable to all situations due to the outpatient

			setting. The EAC has added additional text to this section for further clarity.

Issue 59

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 41 Study characteristics paragraph 1. Omission of “time to stoma reversal”	Add “time to stoma reversal (6 studies)	Duration of stoma is an additional cost and impact to quality of life to patient. Important data to analyse with regards to a condition which impact stoma reversal.	The EAC has made this amendment and added text to section 4.3 to report the results.

Issue 60

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 41 study characteristics paragraph 4 lines 1-7.	Addition of an acknowledgement with regards to ability for study sizes to be larger. Also acknowledgement with difficulty in ability to run prospective studies	Only 10% AL occurrence rate.	The EAC have added extra text for clarification.

Issue 61

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 38 Over view of methods paragraph 1.	Change to “11 were retrospective and 9 prospective studies”	Some studies were prospective, these numbers provide more details.	Thank you for your comment. The EAC has not made any changes as only one study (Rottoli et al) explicitly

A total of 20 full studies and 3 abstracts were included by the EAC. Most of the included studies were case series studies and did not recruit patients prospectively (table 1).			states that it is a prospective study. One study (Jiminez-Rodriguez) is not clear on whether it is retrospective analysis of prospectively collected data and two studies do not report whether they were prospective or retrospective.

Issue 62

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 41 paragraph 4. "that all studies are at high risk of bias because they are retrospective,"	Change and reassess GRADE as not all studies are retrospective – discussed later	Not all studies were retrospective- review this paragraph and GRADE scores	Thank you for your comment. See response to Issue 61 The EAC has amended the GRADE footnote to be clear that not all studies were retrospective. This does not impact the GRADE assessment however as they method is concerned with whether they are observational studies and does not distinguish between prospective or retrospective.

Issue 63

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 41. "The primary outcome in most studies is successful treatment	Change to The primary outcome in most studies is successful treatment with Endo-SPONGE	Current sentence serves only to highlight the differences in success definition while avoiding to cover	Thank you for your comment.

with Endo-SPONGE however the individual studies have defined success differently or, in the case of 2 studies (Kuehn et al. 2016; Schiffman et al. 2019) did not report a definition for success. For example, Boschetti et al. (2018) defined success as 'closure of cavity to <1cm while Huisman et al (2019) defined success as a reduction of cavity with complete granulation and Keskin et al. (2016) defined success as 'sufficient granulation' (see table 1)"	however the definition of success can vary. Most frequently studies including Boschetti et al. (2018) defined success as 'closure of cavity to <1cm or unable to insert and further Endo-SPONGE. Whereas, other were less well defines with Huisman et al (2019) defined success as a reduction of cavity with complete granulation and Keskin et al. (2016) defined success as 'sufficient granulation'. In the case of 2 studies (Kuehn et al. 2016; Schiffman et al. 2019) did not report a definition for success. (see table 1)	frequent definition of 1cm or unable to insert Endo-SPONGE. Suggested sentence is more balanced and representative.	The EAC has amended the text for clarity

Issue 64

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 42, Study Population. "Sample sizes in all of the studies were small, ranging from 3 to 34 patients across the studies."	Change to "Samples sizes were small ranging from 3 participants with the abstracts and from 6 to 34 participantants within the full studies." Include acknowledgment to limitation of sample size to 10% occurrence of AL	Misleading – elsewhere study seems to be referring to 20 full studies not 3 abstracts here data from abstract and study combined. Lack of acknowledgement of ability to gain larger sample sizes is misleading as a study with >20 participants would require over 200 surgeries to occur for rate of leak to be observed.	The EAC has amended the text to reflect the numbers from abstracts and full studies. The EAC has not added any comment on the small sample sizes as this is discussed elsewhere.

Issue 65

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 43 Study population paragraph 2. Omission of no sedation requirements	Add to end of paragraph “One study (Kuehn et al 2016) reported placement and exchanges of sponges without any sedation or anaesthesia”	Currently use of sedation and anaesthesia discussed although this information is missing, inclusion provides full information form included studies.	The EAC has made this amendment

Issue 66

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 42 Study population paragraph 2 lines 1-3. “Across the studies the decision to treat as an inpatient or outpatient and the use of sedation varied and appeared to be based on clinical decision regarding suitability”	Include list of all studies here	Consistency with the rest of the report e.g. time to diagnosis list all papers as does chemotherapy use. Omission here is not consistent with the rest of the text in this section	The EAC has made this amendment

Issue 67

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 44 Concurrent or additional treatments. "Antibiotic use alongside Endo-SPONGE was reported in 6 studies (Katz et al. 2018; Milito et al. 2017; Riss et al. 2009; Rottoli et al. 2018; Strangio et al. 2015; Weidenhagen et al. 2008)"	Change to "Antibiotic use alongside Endo-SPONGE was reported in 6 studies for some patients……..	Not all patients in each of these studies were treated with antibiotics. Some studies are unclear on antibiotic use not actually providing numerical data.	The EAC has made this amendment

Issue 68

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 45 paragraph 1 lines 3-6. "Clinical expert advice suggests that this surgery type may be a contraindication for Endo-SPONGE treatment."	Delete or add in "this is not a listed contraindication with in the instructions for use of Endo-SPONGE"	IFU **Contraindications** Malignant tumor wound. Necrotic tissue/gangrene. Untreated osteomyelitis. Sponge position directly adjacent to vessels, urinary bladder or small intestinal loops. Non-drainable septic focus Clotting disorders. Treatment with a therapeutic dose of anticoagulant drugs. Generalised peritonitis. This is not a contraindication.	The EAC consider it is not appropriate to delete the comment made by the clinical expert. The EAC has amended the text as follows: One clinical expert raised concern as to whether this surgery type may be a contraindication for Endo-SPONGE treatment although it is not listed as such in the Instructions for Use.

Issue 69

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 45 section 4.1 first paragraph. Multiple studies report outcomes of interest including overall success rate (21 studies), stoma/ileostomy reversal and/or restoration of bowel continuity (15 studies), number of treatment sessions/sponges (19 studies), treatment duration (15 studies), complications (11 studies), length of hospital stay (3 studies) and quality of life (2 studies).	Add data from above issues with with regards to paragraph 1 on page 41. The data does not match and data in above issues have addressed these point already	Issues above cover this point. Consistency of data within the report.	Thank you for your comment. The EAC has checked and corrected the data where appropriate.

Issue 70

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 45 success rate. Pooled result from 21 studies was 279/328 (85%) but the range from the individual studies was 40% to 100%.	Add 95% CI of pooled percentage results	Range and pooled data alone is a limited analysis of data, addition of 95% CI allows more information rather than range alone	The EAC did not calculate the 95% CI. No formal meta-analysis of the data was done as without direct comparator studies and considering the high risk of bias in the studies that are available, the EAC does not consider it to be a appropriate. The EAC have provided a pooled result and range simply as an indication of the variation across studies

Issue 71

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 45 success rate. "and one study in patients with IPAA (Wasmann et al. 2019))."	Remove IPAA is not contraindicated. What is the reason for addition here?	The company assume this paper is highlighted due to use for IPAA, it was implied by the EAC that Endo-SPONGE was contraindicated for IPAA this is not the case and the company question why this paper was added.	The EAC has not made any changes. The EAC did not imply that IPAA is a contraindication. Advice from one clinical expert suggested that it may be contraindicated. For this reason this study was included by the EAC and the population clearly identified as patients with IPAA to facilitate clinical discussion around whether IPAA is a contraindication and if not, is there any differences between IPAA and non-IPAA patient populations which may impact outcomes. As noted for issue 70 the EAC has amended the text to clarify that the IFU do not contraindicate IPAA.

Issue 72

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 46 success rate end of top paragraph.	Remove	IPAA is not contraindicated for Endo-SONGE all reference to this should be removed from report as this ias based on opinion and on the	Thank you for your comment.

"but this was in patients with IPAA which may not be a relevant patient group."		Instructions for use of Endo-SPONGE	The EAC has not removed this (see previous comments).

Issue 73

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 46 Success rate. "In one study with 20 patients (Huisman et al. 2019) surgical closure of the defect was performed after a median of 2 Endo-SPONGE changes in 3 patients with the aim of reducing the duration of Endo-SPONGE therapy."	Remove	The company question the relevance of this sentence with regards to success rate.	Thank you for your comment. The EAC has not removed this, although it does not strictly relate to success rate for cavity closure, the study was assessed whether Endo-SPONGE shortened the time to surgical closure. Therefore it is important to report this information as there may be clinical situations where Endo-SPONGE is used as in addition to current treatment and consider this to be a point for discussion for the committee.

Issue 74

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 46 Stoma reversal. "Pooled result from 14 studies reporting reversal of stoma or ileostomy was 144/188 (76.59%)	Add 95% CI of pooled percentage results	Range and pooled data alone is a limited analysis of data, addition of 95% CI allows more information rather than range alone	The EAC did not calculate the 95% CI. No formal meta-analysis of the data was done as without direct comparator studies and considering the high risk of bias in the studies that are available, the

but the range from individual studies was 38.5% to 92.3%."			EAC does not consider it to be a appropriate. The EAC have provided a pooled result and range simply as an indication of the variation across studies

Issue 75

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 49 Complications. "Three studies (Jimenez-Rodriguez et al. 2018, Milito et al. 2017, Wasmann et al. 2019) reported no complications"	Change to Six studies. (Arezzo et al 2015, Boschetti et al 2018, Jimenez-Rodriguez et al. 2018, Milito et al. 2017, Riss et al 2009 Wasmann et al. 2019) reported no complications	To include the additional studies omitted above.	Thank you for your comment. The EAC has not made this change. Three studies explicitly report that no complications occurred, however the remaining studies did not specifically mention recording complications therefore the EAC cannot assume that no complications occurred although this is likely.

Issue 76

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 49 Length of stay. "Length of hospital stay was reported in three studies"	Change to "Length of hospital stay, for in patient use only, was reported in three studies"	Length of stay is only applicable when patients are treated as an in-patient, as discussed above by EAC in report a number of studies where patients were treated as out patients, this information would not be included in this data set and	The EAC has amended the text to reflect this comment.

		reader should be aware and reminded again at this point.	

Issue 77

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 50/51 Table 2 GRADE. Study design	Include prospective change as per row heading requires	The company count N=7 prospective observational studies	Thank you for your comment. The EAC note that only one study explicitly states that it is prospective while one study is not clear. Two studies do not report whether they are prospective or retrospective. The remaining studies are retrospective. The GRADE footnote has been amended – see previous comment relating to this issue.

Issue 78

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 50/51 Table 2 GRADE Explanations a.	Change as n=7 prospective studies – view impact on not all studies being retrospective and review impact on GRADE score	The company count N=7 prospective observational studies, this may alter GRADE a little	Thank you for your comment. See previous comments

Issue 79

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 50/51 Table 2 GRADE Explanations b. "All studies have small sample sizes due to the fact that anastomotic leak is not a common occurrence after colorectal surgery"	Propose some flexibility in the view to sample size with relation to the constraints of the condition. Propose review how small sample number per study, is impacting data critique over pooled data.	Pooled data from all studies n=350 patients, while each study is small with respect to study standards, the overall accumulation of data pooled adds strength and indicative of over 3500 surgeries taking place	Thank you for your comment. The EAC has not made any change to GRADE as footnote b already states that anastomotic leak is a rare event. The EAC also provided a pooled result to show the total numbers although formal meta-analysis has not been performed.

Issue 80

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 50/51 Table 2 GRADE Explanations C. and overall success inconsistence	Review of consistency as serious in light of justification Express mean and 95%(CI) within explanation of c	Range quoted by EAC 56% to 100% without provision of 95% CI. The company provide a weighted mean success rate of 88.8% (95% CI of 85.2-92.4), whilst limitation of the methods used by the company are acknowledged, the addition of 95% CI provide more information and indicate analysis of mean (without weighting) provides a mean of 85.5% (95% CI 79.6-91.6). Only two studies report success below 70% and the company express that lack of expressing on 95% CI by the	Thank you for your comment. The EAC considers that it is important that the range across the studies is presented in order that committee members can discuss the possible reasons why some studies have lower success rates. The EAC acknowledge and accept the company statement that not presenting confidence intervals might be misleading however the EAC have not conducted a

		EAC is reducing the strength of the multiple studies demonstrating high success rate of Endo-SPONGE and can be misleading to the reader.	formal meta-analysis as discussed previously.

Issue 81

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 46 Stoma reversal. Omission of overall analysis	Addition of overall n/total stoma reversed – the company provided 238/277 (85.9%), the EAC have submitted different papers and may differ.	Good description but lack of pooled data with addition of 95% CI to provide a pooled success outcome measure for stoma reversal. Consistency polled data provided for other parameters	Thank you for your comment. The EAC did not calculate the 95% CI. No formal meta-analysis of the data was done as without direct comparator studies and considering the high risk of bias in the studies that are available, the EAC does not consider it to be a appropriate. The EAC have provided a pooled result and range simply as an indication of the variation across studies The EAC has added further detail to this section relating to time to stoma reversal for added clarity.

Issue 82

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 50/51 Table 2 GRADE Explanations i. "Non comparative case series studies, small sample sizes"	Remove "small sample sizes"	Repetition of Explanations b. Explanations i. is used in conjunction with b. in the table.	The EAC has made this amendment

Issue 83

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 50/51 Table 2 GRADE Explanations m.	Needs to be added	Explanation "m" is in the table but not in the list of explanations	Thank you for your comment. The EAC corrected this. The footnote should be 'L'. There is no footnote 'm'.

Issue 84

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 50/51 Table 2 GRADE Explanations j. Reported as a median in two studies and a mean in one study. Mean length of hospital stay	Remove "Mean length of hospital stay indicates a much higher possible length of stay."	Mean is only useful if data is normally distributed. Addition of this statement raises the validity of the median data which is misleading	The EAC has made this amendment.

indicates a much higher possible length of stay.			

Issue 85

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 50/51 Table 2 GRADE. Overall success rate and stoma reversal	Review both	21 and 15 papers available for these outcomes covering 277 and 183 patient (from company submission, number may differ slightly for EAC data) high number of total patient and smaller 95% CI range compared with range warrants a review of assessment of this data.	Thank you for comment. The EAC has checked the numbers throughout the report for consistency.

Issue 86

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 52 Table 3. Arezzo “89% (9/10) in acute leaks (<60 days)”	Replace “90% (9/10) in acute leaks (<60 days)”	Inaccurate data	The EAC has made this amendment

Issue 87

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 53 Table 2. Huisman stoma reversal/ bowel continuity “70% (14/20)”	Add “bowel continuity was restored in 70% (14/20) and stoma reversal occurred in 14/18 (77.8%) of patients	Only 18 Patients had a stoma “two patients received Endo-SPONGE therapy without diverting ileostomy” currently not clear with multiple items in column title	The EAC has amendment

Issue 88

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 53 Table 2. Omission of stoma closure time	Add column for time to stoma closure	Currently missing informative information on time to stoma reversal – this has direct impact on NHS costs and patient quality of life	The EAC has added time to stoma reversal to the stoma reversal column.

Issue 89

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 54 Table 2 Jiménez Rodríguez. Complications in 2 patients (both from the anterior resection with ileostomy group), closure was not	Replace with n=1 stenosis, n=1 chronic fistula and n=1 osetomylitis	Need for additional surgery is not a complication but rather, this would be standard practice if non-surgical route were not successful.	Thank you for your comment. The EAC has clarified this information in the report.

achieved, necessitating surgical intervention			

Issue 90

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Table 3 Page 55 Kuehn. Overall success "(non reported)"	Remove	Looks like a typing error as success rate reported in table	Corrected

Issue 91

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Table 3 Page 56 Mussettos. Time to treatment completion	Add "median treatment duration 37 days (18-65)"	In text of study	Added

Issue 92

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Table 3 Page 57 Riss. Overall success rate missing	Add "initial success of closure of anastomotic leak 20/23 (87%)" Long term continued success 15/20 (75%)	Study looks at long term success although discusses initial success/failure rate which can be added to the study – if concern re duplication of Riss 2009 then only add the long term continued success rate.	Thank you for your comment. The EAC has added the long term success data to the table.

Issue 93

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 67 Evidence synthesis and meta – analysis Paragraph 3. "The EAC note that the evidence base (published studies) used in the company evidence synthesis is largely the same as that used in the published reviews"	Remove	Evidence base used in company submission for meta-analysis are based on company literature search also have much similarities with the EAC as well as previous meta-analysis as there is a limited supply of paper with Endo-SPONGE. Could the EAC really expect much difference? The company did not use the exact same studies as previous meta –analysis we had different excluding criteria.	Thank you for your comment. The EAC has deleted this but has added extra detail. This was not a criticism of the company submission. It was intended to highlight the degree of agreement between the company submission, published studies and the EAC selected studies so that the committee could be clear that essentially there is a limited evidence base and everyone is using the same key published studies.

Issue 94

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 58 paragraph 1 last line" (See section 5.3)."	Double check – there is no section 5.3, should it be 8.3?	Cannot find section 5.3 , tying error	Thank you for your comment. The EAC has made this correction.

Issue 95

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 68 Paragraph 2. Pooled analysis indicates an 85% success rate for Endo-SPONGE but the range from individual studies was 40% to 100%.	Add 95% CI Also add the company added pooled data along with weighted men in their meta – analysis, although weighted mean was referred to in the text.	Addition of 95% CI adds more reference when range and median are already included. We expressed both pooled data and weighted mean for full transparency and chose weighted mean in the text. Minimal difference was observed between them.	Thank you for your comment. The EAC have added the company 95% CI's here however have not added anything else as the EAC did not calculate 95% CIs (see previous comments)

Issue 96

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 68 paragraph 2. This compares well with the company evidence synthesis which suggest an 88.8% success rate (weighted mean) but again a wide variation across individual studies (56% to 100%).	Add (95% CI 85.2-92.4)	Addition of 95% CI adds more reference when range and median are already included.	The EAC has added the 95% CI's for the company analysis.

Issue 97

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 68 paragraph 3. "From these 3 studies (Blumetti et al 2014; Damreur et al 2009 and Felder et al 2014) the rate of success for PD is 70% (the range is 29-82%)"	Change to …….rate of success for PD is 63.2% (the range 29-79%)"	Blumetti success 43/75 Damrauer success 5/17 Felder success 50/63	EAC review of the papers suggests that the numbers are: Blumetti: 26/40 Damrauer: 4/14 Felder: 50/61 As mentioned in the report, the company submission provides no detail of how they have extracted numbers from the comparator studies and the EAC therefore cannot verify the values provided by the company. The data used by the EAC related specifically to the use of percutaneous drains as this is what the company presented in their economic model. The EAC therefore judged that it would be useful to report the PD drainage data. For example, the numbers used from Blumetti et al are taken from table 3 of the publication, rows for percutaneous drainage only (non-operative management of leak) as this was considered the most appropriate. The EAC note that the scope relates to extra-peritoneal leakage only however due to the lack of data for PD alone, has

			included all extra-peritoneal and intraperitoneal data here but note that this may impact the results.

Issue 98

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 68 Paragraph 3. "Which seems closer to the success rate of Endo-SPONGE suggesting that treatment with PD has similar effectiveness to Endo-SPONGE."	Remove or reword	EAC suggest Endo-SPONGE success rate is 85% (range 40-100%) and PD is 70% (range 29-82%), These results are not similar and show a shift in the positive for Endo-SPONGE. The company highlight that EAC has provided no 95% CI to their results, Addition of 95% CI for Endo-SPONGE highlights how the range is misleading.	The EAC has added some clarity to this section.

Issue 99

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 68 Paragraph 4. "For stoma reversal rates, the EAC pooled analysis indicated that stoma reversal occurs in approximately 77% of patients (range 38.5% to 100%)"	Add 95% CI.	Pooled data and ranger offer limited information, 95% CI offers detail on where majority of data lie.	The EAC have deliberately steered away from providing 95% CI intervals. The pooled result with the range is intended to give a very broad impression of the data as formal meta-analysis was not considered to be suitable.

			The EAC has included the company 95% CI's where appropriate for reference.

Issue 100

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 68 Paragraph 4. "Company analysis which suggests a 79% success rate (weighted mean) with a range of 38% to 92%."	Add (95% CI 71.9-86.1%)	Pooled data and range offer limited information, 95% CI offers detail on where majority of data lie.	As above

Issue 101

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 69 Paragraph 1. "The EAC report a rate of 82% (50% to 94%) for stoma reversal however this is based on data from only two studies (Harris et al 2010; Sirois-Giguere et al 2013)"	Change to "…..Rate of 63% (30% to 93%)…… add Damrauer et al 2009	Add data from Damrauer et al n=14 treated with PD, free leaks n=1/4 success rate (25%), contained leaks n= 3/10 (30%) overall 4/14 (29%) (Described in text of study). Contained leaks most suitable to use Harris et al = 2/5 stoma reversal from PD 40% described in diagram Sirois-Giguere = 93% for TD (n=14/15)	Thank you for your comment. The EAC has made changes to the text here. The EAC had not included Damrauer initially as it was unable to validate which data from the study had been used in the company submission and why. The EAC were aware that Damrauer reported data for free leaks and contained leaks but as the company

		Pooled data n=19/30 63% Data based on re-reading studies for fact check, the company acknowledge these data differs from company submission due to sole focus on PD here and non operative focus in company submission.	submission had not provided any rationale for data extraction, it was unable to verify the choice of data. The EAC calculate that Sirois Giguere values are 15/16 (table 2 of publication suggests 16 patients received transanal drainage with a 93% success rate (table 4) (14.88 people rounded up to 15). There will be some discrepancies due to rounding but the addition of Damraeur results in a rate of 64%.

Issue 102

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 69. "…….PD studies only (82%) and is towards the lower end of the range for both suggesting that surgical treatment may result in lower stoma reversal rates. "	Change to "….PD studies only (63%)….."	EAC data queried in 102.	Thank you for your comment. The EAC has added text here for clarity.

Issue 103

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 69.	Remove – all queries were clarified by company, any other queries were not raised.	The company was requested to clarify on two referencing concerns and provided corrected references,	Thank you for your comment.

"There were also a number of issues and inconsistencies with referencing throughout the company submission, both clinical and economic which made it difficult for the EAC to match data with the correct studies."		one due to a website re-arrangement and another was error in reference website provided.	The EAC agree that any queries put to the company were answered. The inaccuracies here relate to data extraction from individual studies and studies listed in reference lists. Due to limited time, the EAC does not generally contact the company to verify the details of data extraction as it is expected that this will be provided in the company submission.

Issue 104

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 70 paragraphs 1. "While a second clinical expert suggests that IPAA would not be a contraindication."	Add on end – "the Instructions for use do not list IPAA as a contraindication"	The IFU should be quoted here as factual reference to contraindications rather than opinion.	The EAC has added text relating to the IFU but has not removed the text relating to clinical opinion as this is important for discussion.

Issue 105

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 70 end of paragraph 1. "The EAC suggest that this should be given consideration in relation to NHS patients."	Remove	IPAA is not a contraindication for Endo-SPONGE, this is one opinion and conjecture.	Thank you for your comment. The EAC has not removed this as this was a comment from a clinical expert. The clinical expert was clear that this was an opinion and IPAA was not definitively a contraindication.

			It is important that the committee are given the opportunity to discuss this and draw their own conclusions based on the whole body of evidence which includes clinical opinion.

Issue 106

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 70 Paragraph 3. "The published evidence does not suggest that Endo-SPONGE would be used as a replacement for antibiotics"	Change to "The published evidence is unclear Endo-SPONGE would be used as a replacement for antibiotics"	Only 6 studies mention use of antibiotics before or during Endo-SPONGE therapy, number of patient using antibiotics n=21/116 patients included in these 6 studies.	The EAC has made this amendment

Issue 107

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 70 paragraph 3. "The published evidence does not suggest that Endo-SPONGE would be used as a replacement for antibiotics with a number of studies indicating that antibiotics were used alongside Endo-SPONGE"	Change to "The published evidence does not suggest that Endo-SPONGE would be used as a replacement for antibiotics six studies indicating that antibiotics were used in advance or alongside Endo-SPONGE for n = 21/116 patients in these six studies"	Only 5 studies "a number" is in accurate. Antibiotics were used before Endo-SPONGE. Not all patients in these studies always received antibiotics.	Thank you for your comment. The text has been amended for clarity.

Issue 108

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 70 paragraph 4. "The EAC note that in many studies, use of Endo-SPONGE was associated with inpatient treatments and involved general anaesthetic"	Remove and replace "the EAC note that use of Endo-SPONGE is associated with both inpatient and outpatient use, as well as involving, general aesthetic, sedation and no sedation at all".	Misleading, this reads as many patients were treated under general anaesthetic – the studies do not show this. On page 42 the EAC list 6 studies involving light sedation and outpatient treatment while only mentioning 1 paper discussing use of general anaesthetic, this conclusion is not consistent with the report and the studies. The replacement statement is inline with page 42 and all studies, including those using non sedation, currently omitted by the EAC here and on page 42.	Thank you for your comment The EAC has added text for clarity.

Issue 109

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 71. Integration into NHS "One clinical expert suggests that Endo-SPONGE is labour intensive for the surgeon and the patient."	Please clarify how experienced the expert is with using Endo-SPONGE	All medical devices have a learning curve, to describe use of Endo-SPONGE as labour intensive indicate a lack of familiarity with the device as studies indicate a 15 Minute insertion time on average, though this will depend on	Thank you for your comment. The EAC have not removed this as this was from a clinical expert. It is not the role of the EAC to comment on the level

		experience of clinician and patient medical condition.	of experience of the experts providing their clinical opinions. This will be something the committee will discuss while considering all of the available evidence.

Issue 110

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 81 8.4 scenario 1. "Information from the clinical experts and from the literature suggests that patients being treated with Endo-SPONGE will have at least one inpatient appointment with general anaesthetic."	Change to "……. With general anaesthetic or sedation"	Literature does indicate that an inpatient stay will be required for initial placement, however use of general anaesthetic was mentioned in only 4 studies, definitively for 15 patients in three studies only and descriptively alongside sedation as possible. Although this will not impact the economic outcome.	Thank you for your comment. The descriptions of scenarios have been clarified

Issue 111

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 82 bullet point 3. "all subsequent Endo-SPONGE procedures are carried out with the need for general anaesthetic in an outpatient setting **or** if the patient is already an inpatient, Endo-SPONGE procedures are	Replace with "…….carried out without the need for general……."	Should this say without general anaesthetic for secondary placements?	Thank you for your comment The descriptions of scenarios have been clarified

still carried out without general anaesthetic and not in a theatre setting”			

Issue 112

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 83 Scenario 1 bullet point 5. “and endoscopy reference costs for an outpatient setting”	Add (including staff time)	Staff time included in theatre time BUT not endoscopy reference costs, unsure why these are not consistent and may skew costs on secondary placements.	NHS reference costs are a standard source of cost information, and will always use reference costs. The wording has been amended for clarification

Issue 113

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 84 Scenario 2 bullet point 4. “Costs incurred for subsequent placement include the cost of Endo-SPONGE equipment and day case endoscopy costs”	Add (including staff time)	Staff time included in theatre time BUT not endoscopy reference costs, unsure why these are not consistent and may skew costs on secondary placements	As above

Issue 114

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 83. "Discussion with clinical experts indicated that there is a possibility that patients will have a percutaneous drain and Endo-SPONGE treatment. The EAC have therefore modelled a scenario where the patient has investigation for AL in theatre under general anaesthetic, with the option to place Endo-SPONGE at the same time. A percutaneous drain is also placed at the same time"	Remove scenario	In all of the company experience we have never known of Endo-SPONGE to be used in conjunction with percutaneous drain. Suggest this is very unlikely scenario and should be removed from the EAC economic analysis.	The scenario was included in response to expert comments. This gives the committee information to inform their discussion if they feel it is a possible scenario. The EAC are not recommending it as a base case, but as an exploratory analysis.

Issue 115

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 85 success rate for non surgical treatment. "Reported but from 3 studies the rate of success for PD is 70% (the range is 29-82%). The EAC base case therefore assumes that 70% of PD treatments are successful."	Change to …….rate of success for PD is 63.2% (the range 29-79%)"	Covered previously in issue 98 Blumetti success 43/75 Damrauer success 5/17 Felder success 50/63	Thank you for your comment. Please see response to issue 97 and 98

Issue 116

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 85. Proportion of patients treated non surgically…	Add “The company responds that 6 studies discuss use of Endo-SPONGE in AL with a cavity size greater than 10cm (for some patients) and argue that PD would not be used in these patients. While the companies assumption cannot be verified the company stand by their claim that patients with larger leaks could be treated with Endo-SPONGE co pared with PD hence there should be a difference in patient number between the two pathways,”	Endo-SPONGE can be used in large leaks (Stangrio, Weidenhag, Boschetti,Milito and Musesettos)	Thank you for your comment. The EAC does not disagree that Endo-SPONGE may be suitable for patients in whom PD would not however as this assumption cannot be verified. The EAC has presented results for a scenario whereby there is no difference in the number of patients who could be treated with Endo-SPONGE for discussion. It is important in the absence of published data that the committee has information on what changes would impact the economic outcomes. The EAC has added additional analysis using the company clinical inputs with the EAC proposed costs, and amended the text in the report to reflect the uncertainty.

Issue 117

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Table 5.	Propose decrease in light of issue 117	As above in issue 117	Thank you for your comment.

EAC value non-operative on current pathway, 62.8%			Please see response to comment above.

Issue 118

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Table 5. EAC value success non-operative pathway 70%	63%	As issue 116 and 98	Thank you for your comment. Please see response to issue 98 and 116. The EAC acknowledge that the success rate on the non-operative pathway may not be as high as 70% however this will be accounted for in sensitivity analysis.

Issue 119

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Appendix E.	Change in accordance to earlier issues listed above.	Change in accordance to earlier issues listed above.	Thank you for your comment. No update is required, however results including analysis using company clinical inputs are included in the tables of the main report.

Issue 120

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 89 Table 6.	Change in accordance to earlier issues listed above.	Change in accordance to earlier issues listed above.	Table 6 compares the impact of alternative clinical inputs. The text has been altered to reflect the uncertainty around these inputs.

Issue 121

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 90 Table 7. Endoscopy unit per treatment - unknown (link not access online)	Remove	This query was validated by the company when requested by the EAC.	Thank you for your comment. The EAC has updated this text.

Issue 122

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 90 Table 7 Percutaneous drain, link not functional.	Remove	This query was validated by the company when request by the EAC.	Thank you for your comment. The EAC has updated this text.

Issue 123

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 96 paragraph 1. "As a result, the changes made by the EAC result in Endo-SPONGE becoming cost incurring in year 1 (-£1,141.10) compared with percutaneous drainage."	Update as required by earlier issues.	Earlier issue may alter data used.	The text has been altered to reflect the uncertainty around the different clinical inputs and the associated results. Results have been presented using both the company and EAC clinical inputs.

Issue 124

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Tables 5-10.	Change as required per earlier issues	See earlier issues	The text has been altered to reflect the uncertainty around the different clinical inputs and the associated results. Results have been presented using both the company and EAC clinical inputs.

Issue 125

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Table 11 Scenario 3.	Remove as per earlier issues	See earlier issues	See previous comments (issue

Issue 126

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 98 paragraph 2. "Clinical advisers have described the Endo-SPONGE procedure as labour intensive."	Make singular, remove plural.	Earlier in report, labour intensive was reported by only one clinical advisor and the company have questioned the experience of the singular view.	The EAC has made this change

Issue 127

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 101 Paragraph 3. "and it is unclear whether Endo-SPONGE would be used in such patients in the UK."	Remove	As discussed earlier this is opinion of one person's and IPAA is not contraindicated for Endo-SPONGE.	The EAC has added text for clarity

Issue 128

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Appendix B	Update as per any earlier issues		Table has been updated.

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Issue 129

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Appendix D	Update as per any earlier issues		No update required, this is a record of some of the EAC testing process, not a results table