National Institute for Health and Care Excellence

Medical technologies evaluation programme

MT461 Endo-Sponge for treating rectal anastomotic leakage

Consultation comments table

Final guidance MTAC date: 18th September 2020

There were 44 consultation comments including 7 duplicates from 4 consultees:

- The manufacturer submitted 33 comments
- A professional organisation submitted 1 comment
- A healthcare professional submitted 10 comments

The comments are reproduced in full, arranged in the following groups – (list groups used, for example, clinical use, cost considerations and miscellaneous).

#	Consultee ID	Role	Section	Comments	NICE response DRAFT/FINAL
Recommendation (comment 1 to 11)					
1	1	Manufacturer	1.1	There is a wealth of retrospective data and peer reviewed data available, showing that Endo-SPONGE is safe and effective for the management of AL. It would be impossible to conduct an RCT for this patient population, and the EAC have also confirmed this, in their opinion. I believe it is unfair to state there is not enough good quality evidence. Existing data has been subjected to peer review, and has this therapy has shown to be a safe and effective option for managing grade 1 and grade 1 AL. This device would never be used as routine, but I do believe it could and should be recommended as a safe and effective option for the treatment of grade 1 and grade 2 AL.	Thank you for your comment. The committee considered your comment carefully and considered that further research using real-world data would be valuable to define patient selection and assess the effectiveness of Endo-SPONGE compared with other treatment options. The committee decided not to change the guidance.

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2	1	Manufacturer	1.2	It would be very difficult to obtain meaningful data of this type, given that the patient population is limited, however the existing data does reflect the efficacy of the product. The IFU states very clearly which patients are most likely to benefit from Endo-SPONGE, and typically would fall into patients categorised as having grade 1 or grade 2 ALs. Patient reported Outcome Measures were only recently introduced, and have not been widely adopted as part of clinical audit so far, but agree that this should be included in ongoing analysis, but should not preclude endorsement of this device, as a safe and efficacious treatment option for this condition. Truth is that there is not yet any standardised clinical pathway for the management of ALs, so comparative analysis against other therapies or treatment options is very difficult.	Thank you for your comment. The committee considered your comment carefully and acknowledged the grading system but the clinical experts advised that the system is not widely used in routine practice. The committee decided not to change the guidance.
3	1	Manufacturer	Rationale	There is a wealth of retrospective data and peer reviewed data available, showing that Endo-SPONGE is safe and effective for the management of AL. The product IFU cleraly states which patients would benefit most from using the device, and typically these patients would fall into grade 1 and grade 2 ALs. It is unfair to state there is not enough good quality evidence. Existing data has been subjected to peer review, and has this therapy has shown to be a safe and effective option for managing grade 1 and grade 1 AL. The lack of a standardised clinical pathway makes financial modelling very difficult, however there is good evidence to show that it can reduce length of stay, improve rates of stoma reversal and reduce the need for further surgical intervention.	Thank you for your comment. The committee considered your comment carefully and understood the quality of the evidence base is low due to the small sample size and heterogeneity in the treatment pathway. Additional real-world evidence on the technology will be valuable to assess the effectiveness of Endo-SPONGE compared with other treatment options. The committee decided not to change the guidance.
4	1	Manufacturer	4.3	Real-world evidence would be difficult to obtain as current ALs are not recorded in hospital episode statistics. Going forward, the creation of a registry would be beneficial in terms of gathering RWE, as well as patient-reported outcomes, and possibly as a tool for defining a standardised clinical pathway for managing AL.	Thank you for your comment. The feasibility report commissioned by NICE concluded that the creation of a registry to capture real-world evidence will help address the uncertainties around treatment pathways. Final NICE guidance recommends the collection of this type of evidence.
5	1	Manufacturer	4.4	I believe that the quality of data was judged as poor, and at risk of bias due to the lack of any RCTs, however, as noted previously, it is highly unlikely that any such data could be achieved with this patient population. However we agree that the formation of a registry would be beneficial in terms of gathering RWE, as well as patient-reported outcomes, and possibly as a tool for assisting to define a standardised clinical pathway for managing AL.	Thank you for your comment. The quality of the evidence base was assessed by the independent external assessment centre using well established and validated appraisal tools. Study design is only one aspect of quality assessment. The evidence base for Endo-SPONGE was

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					limited in other aspects including but not limited to the heterogeneity of included populations, variability of clinical outcomes, small sample sizes. The committee understood the limitations of conducting RCTs in this patient population and pathway and recommended gathering real-world evidence to address the remaining uncertainties.
6	2	Manufacturer	1.1	This recommendation is based on a lack of evidence, which for a complicated and rare condition will unlikely to be achievable and discussed repeatedly below. The experts consulted agreed that Endo-SPONGE is a benefit to patients who have already under gone long surgery and may prevent further surgery and is a useful adjunct to treatment. Clinicians should have access to safe equipment with a good safety profile. Endo-SPONGE has 0.014% complaints per device used globally, no field safety notices and low adverse event reporting in the literature. The EAC also conclude "Endo-SPONGE appears to be a safe and effective non-surgical way to manage anastomotic leaks" There is no current "routine" treatment for this subset of patients - due to the complexities there are broad guidelines set out by the ACPGBI, but the treatment is always very patient specific and based on an individual basis. Endo-SPONGE, like any treatment for anastomotic leak, would not be routinely adopted, but rather, as with other non-surgical interventions which may save the need for a patient to have surgery, should be available and considered for treatment. Currently in section 3.3 of this report NICE report that "the limited evidence suggests that Endo-SPONGE could be considered as a treatment option for anastomotic leakage." Respectfully request NICE to consider the phrase here to be more reflective of case by case basis by which anastomotic leaks are treated and allow for Endo-SPONGE to be "considered for use on a case by case basis, for patients with a contained anastomotic leak of the low pelvic area."	Thank you for your comment. The committee considered your comment carefully and acknowledged that Endo-SPONGE is a treatment option for some people who had anastomotic leakage after rectal surgery. Currently there are no clear eligibility criteria and further research using real-world data would be valuable to define the patient selection. The final guidance outlines the anatomical and patient-related factors that are likely to be considered when treating anastomotic leaks in section 4.1. The committee decided not to change the guidance.
7	2	Manufacturer	1.2	not be achievable in this patient group." Additional good quality research is unlikely to be attainable. The EAC also concluded "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." In addition the EAC also conclude "Anastomotic leak is a rare occurrence therefore the study sample sizes are	Thank you for your comment. The committee considered your comment carefully and acknowledged that Endo-Sponge is safe, well-tolerated and effective therefore should be considered as an option for use for a selection of patients

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				small. While this methodologically impacts the quality of the studies, it should be highlighted that larger study sample sizes would Expert opinion in the initial MIB states "comparative trial design is also challenging because it raises ethical issues around randomising patients at risk of infection and sepsis." The possibility to gain further timely evidence is exceptionally limited and RCT's would not be a viable option. Use of larger real world evidence data bases would not be attainable as there is not a hospital code to record anastomotic leak, hence no ability to identify initial cases from hospital episode statistics (HES), nor to identify treatment pathways. While a registry may help, there is not such registry for anastomotic leaks, any registry for Endo-SPONGE would only afford data on Endo-SPONGE and due to small numbers of patient would take 5-10 years to obtain a reasonable number of patients to overcome the natural heterogeneity of the patient subsets. This recommendation is not achievable.	and it is not feasible to conduct a high-quality RCT as the number of people with anastomotic leakage is small. Further real-world data such as registry data for Endo-SPONGE would improve the evidence base. The committee understood that hospital data on anastomotic leaks is poor in the NHS. It thought the creation of an anastomotic leak registry to capture real-world evidence on all patients with this condition would help address the uncertainty around patient selection and treatment pathways. The committee decided not to change the guidance.
8	2	Manufacturer	1.2	PROMS and patient QoL are newly reported measures and when the long duration studies for Endo-SPONGE commenced these measures were not routinely recorded. Multiple of the submitted studies reference stoma reversal rate with use of Endo-SPONGE. Stoma has a known impact on QoL for patients with closure of stoma preferable. PROMS data for current treatment options for anastomotic leaks are also current unavailable.	Thank you for your comment. The final guidance emphasizes the need to collect data not only on patient QoL but also on stoma reversal rates that has been highlighted as an important outcome. The committee agreed that stoma reversal was an important outcome to measure the clinical effectiveness of Endo-SPONGE relative to other treatments (see section 4.2).
9	2	Manufacturer	1.2	Literature does not include costs of treatment of anastomotic leak by other means, to the granularity of different treatment options used, this makes an economic cost comparison difficult. Ashraf et al 2012, calculated cost of anastomotic leak to be £17,220 SD±£9642. Ashraf et al report an increase in cost for anastomotic leak with conservative treatment costing £9686 ± £2626 and laparotomy costing £20671±£11,301, this costing data was provided by the local commissioning department for all 161 patients undergoing low anterior resection between 2008-2009, of which only 20 had leaks. The small number of leaks makes generating costing data varied as small numbers are impacted by patient heterogeneity. As stated above comparative studies are unlikely to be feasible due to: small number of anastomotic leaks in UK and questions over randomisation. There are currently no hospital reporting code for anastomotic leak and the treatment options are not reported in HES data making the opportunity to generate	Thank you for your comment. The committee considered your comment carefully and understood that the cost quoted in Ashraf et al was not specific to Endo-SPONGE. It understood the difficulties of generating an accurate cost model for this heterogeneous patient group. The committee considered that real-world data collection should be used to inform the cost modelling of Endo-SPONGE compared with other treatments for anastomotic leakage.

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				economic costing from Hospital Episode Statistics (HES) unattainable. There is no national or international anastomotic leak registry to report anastomotic leaks and their treatment pathways to gain and comparative outcome or cost analysis. This recommendation is unlikely to be achieved.	
10	2	Manufacturer	rational	This sentence is misleading. Evidence form observational studies demonstrate that Endo-SPONGE resolves anastomotic leakage, not reduces. If the anastomotic leak is not resolved then surgery is required.	Thank you for your comment. This has been amended.
11	2	Manufacturer	rational	There is no clinical care pathway, however there are guidelines by The ACPGBI, recommending drainage as an option in scenarios 1, 2a and 2b; for grade 1 and 2 leaks (table 6). Endo-SPONGE is a drainage system and fits into "drainage" recommendations.	Thank you for your comment. Please see the response to comment 1.
Technology (comment 12 and 13)					
12	1	Manufacturer		Endo-SPONGE is inappropriate for patients with generalised peritonitis, but there are many examples where patients with Sepsis have still benefited from Endo-SPONGE	Thank you for your comment. General peritonitis or sepsis is listed as contraindications in the instruction for use (v0.9, 11/2019). The final guidance outlines the anatomical and patient-related factors including an individual's clinical condition that are likely to be considered when treating anastomotic leaks in section 4.1.
13	4	Healthcare professional		Disputed contraindications “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.“ This advice runs contrary to the successful application of endosponge in pouch salvage following leaks in the UK and in European high-volume centres, where it forms part of the routine management protocol for leaks and which has been widely published and is well known in the colorectal community. It is not contraindicated in this setting. I note there is dispute between the NICE experts on this point. “One clinical expert suggests that IPAA may be a contraindication while a second clinical expert suggests that IPAA would not be a contraindication”. I would ask for an explanation for the following phrase “The EAC suggest that this should be given consideration in relation to NHS patients.” What does this mean exactly? I would suggest you delete this currently unfounded contraindication or provide further data to support this claim	Thank you for your comment. The committee considered your comment carefully. It noted that the instructions for use does not list IPAA as a contraindication. However, the advice provided by 2 experts during the evidence review was conflicting, and so the EAC highlighted this in the assessment report and concluded that the decision to use Endo-SPONGE in patients with IPAA should be considered by the treating clinician within the NHS setting. More specifically, on page 74 of the AR, it states “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

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					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 suggests that this should be given consideration in relation to NHS patients". The committee decided not to change the guidance.
Patient selection (comment 14 to 15)					
14	1	Manufacturer	4.1	AL occurs in only 6% to 10% of colon surgeries, however the consequencies can be catastrophic. The EAC report states "Based on a review of the evidence the EAC do not consider that further research studies wound improve the quality of clinical evidence at this time. The clinical pathway for management of AL after colorectal surgery is not clearly defined and numbers of patients with this outcome is small." This feedback needs to be taken into consideration. The product IFU clearly identifies which patients would benefit most from Endo-SPONGE. If patients are selected in line with the guidelines outlined in the IFU, most of these patients would fall into the categories of grade 1 and grade 2 ALs.	Thank you for your comment. The committee considered your comment carefully. It understood that the indication in the IFU is that Endo-SPONGE is for treating anastomotic or Hartmann's stump leakages following colorectal surgery in the lower pelvic area. But the evidence base presented the clinical heterogeneity related to population characteristics and the definition of surgical site infections and success. Therefore, the committee agreed that collecting real-world evidence is important to understand which patient population might benefit from Endo SPONGE.
15	2	Manufacturer	4.1	The clinical experts describe the patient subset well in section 4.1 of this NICE recommendation. The ACPGBI guidelines recommend drainage as an option in scenarios 1, 2a and 2b; for grade 1 and 2 leaks (table 6). Endo-SPONGE is a drainage system and fits into "drainage" recommendations. The IFU defines indications for use as "treatment of anastomotic leak or Hartmann's stump leakages following colorectal surgery in the lower pelvic area (extra peritoneal position) by means of negative pressures. The leak must have created a drainable cavity with or without local infection". Amongst the	Thank you for your comment. Please see the response to comments 1 and 14.

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				contraindications is: "generalised peritonitis or sepsis." Clearly identifying the patient selection criteria suitable. Anastomotic leak can lead to severe complications for the patient and treatment options for such severe surgical complications should be based on the surgeon's clinical judgement. The EAC concluded that use of Endo-SPONGE should be based on clinical assessment and discussion between the clinician and patient taking in factors such as severity of leak, patient condition and patient preference. Experts report both in this consultation and for the in initial MIB reported use of Endo-SPONGE in grade 1 and 2 anastomotic leaks. With small number of anastomotic leaks and natural heterogeneity within this patient group, further research will be unlikely to further define the patient criteria which has already been clearly defined by both ACPGBI, the IFU for the device and by expert clinicians here. Treatment of anastomotic leak will always require the expert opinion of the treating surgeon to clinically assess each individual patients' needs.	
Care pathway (comment 16)					
16	2	Manufacturer	2.4	Table 6 from the ACPGBI guidelines should be referred to detailing option suggestions of drainage for grade 1,2 and 3 as Endo-SPONGE is a form of drainage. Currently only the over-arching recommendations and none of the details are provided. Multiple expert advisors referred to these extra details of the guidelines.	Thank you for your comment. The committee considered your comment carefully and understood that the company's cost model structure was based on the grades outlined in the ACPGBI guideline. This has been added in the guidance (section 3.4).
Evidence (comment 17 to 24)					
17	2	Manufacturer		This comment implies all the studies were retrospective this is not the case.	Thank you for your comment. This has been amended to state that most studies were used retrospective design (see section 4.4).
18	2	Manufacturer	4.2	Data from all international studies over the last 10 years has demonstrated results from 276 patients with high "success rates". As many of these studies were retrospective, these success rates were clinical successes obtained from clinical notes (real world evidence) - the patients were deemed clinically to have had their anastomotic leak resolved and as such the clinical end point should not be disregarded if final outcomes measures were defined differently by the various authors. If the Endo-SPONGE had not been successful further treatment would have been initiated e.g. surgery.	Thank you for your comment.
19	2	Manufacturer		Caution advised, referring to the meta-analysis by Mahendran et al as it includes multiple publications which have not used the Endo-SPONGE device but rather	Thank you for your comment. The committee considered your comment

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				other devices which may not be CE marked for the intended use of endoluminal vacuum treatment of anastomotic leaks and does not represent results from using Endo-SPONGE. In addition multiple papers whereby Endo-SPONGE was used and met the criteria were not identified or included. These issues should be highlighted in reference to this paper or reference discarded.	carefully and agreed that the meta-analysis by Mahendran did not change the evidence base significantly. The committee decided not to change the guidance.
20	2	Manufacturer	4.3	The literature submitted demonstrates "discomfort " reported in 22/276 patients (8%), mild pain reported by 5/276 patients (2%) and 2/276 reported "pain" (1%), with only 1/276 patients stopping due to pain (0.5%). Real world evidence would not be currently attainable due to anastomotic leak not being reported in hospital statistics and reporting of device use is not reported in hospital episode statistics, please also refer to earlier comment regarding gaining addition research in this area.	Thank you for your comment. This has been amended to note the number of people who experienced side effects was small (see section 4.3).
21	2	Manufacturer	4.4	Would this be an Endo-SPONGE registry or an anastomotic leak registry? In addition one need to ask the question, would all surgeons be willing and happy to submit data regarding anastomotic leaks?	Thank you for your comment. The committee considered your comment carefully and agreed that a registry on anastomotic leak would be useful to gather real-world data on the use of the technology in clinical practice.
22	2	Manufacturer	4.3/4.4	Current real world evidence is not set up to collect this data, with no means to report anastomotic leaks or treatment in HES data. A registry could be created - would this be an endo-SPONGE registry or an anastomotic leak registry? In order to obtain enough data any registry would need to be international. Data from all international studies over the last 10 years has demonstrated results from 276 patients with high "success rates". These success rates were clinical success rates and similar to that which would be obtained from clinical notes - the patients were deemed clinically to have had their anastomotic leak resolved. Observational data has been submitted here classed as low quality due to small numbers. Does NICE believe it is achievable to gain extra "observational and real world data" from the UK considering the small number of cases per year, (maximum 10% of low arteria resections result in an anastomotic leak)?	Thank you for your comment. Please see the response to comment 21.
23	2	Manufacturer	4.5	Is it appropriate to use an estimate here when there are numerous publication referring to anastomotic leak rate? A reference here is more suitable than an estimated opinion	Thank you for your comment. The committee considered your comment carefully and acknowledged that the anastomotic leaks rates varied in the published evidence. A range of the leak rate was added in the guidance (see section 4.5).

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24	4	Healthcare professional		Criticism of the quality of the scientific literature in anastomotic leaks - I note the EAC investigators criticise the quality of the 20 or so studies in the literature on endosponge but rely on small and very old literature (3 studies) evaluating percutaneous drainage. “The EAC note that 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%). The EAC base case therefore assumes that 70% of PD treatments are successful.” The values in outcomes in these studies are vastly different. This seems deeply flawed methodology and likely will not represent true outcomes in the contemporary NHS. - The EAC repeatedly criticises the literature on Endosponge but states “however due to the small number of patients who develop anastomotic leak it is unlikely that the quality of evidence can be improved.” Your conclusion about the lack of evidence could potentially be applied to the entire field of therapy in anastomotic leaks. We then reach the unhappy situation to query therefore if NICE can advise on any management in this field when your own analysis suggests it may not be possible to generate this high quality research. NICE must presumably have a responsibility to take a pragmatic view of the evidence to advise UK clinicians. The implied criticism of the technology for the lack of high quality research, whilst admitting that there is an inability to perform that research, is unhelpful. The case for future research and a national database is however well received.	Thank you for your comment. The committee considered your comment carefully and acknowledged heterogeneity in the study population and outcomes reported. The final guidance acknowledges that it is unlikely that it would be practical to do a randomised controlled trial. The committee agreed further data collection would be valuable to improve the evidence base for the technology. They suggested that using a national database or clinical registry could help evaluate the clinical benefits of Endo-SPONGE and define the most appropriate patient population.
Cost model (comment 25 to 35)					
25	1	Manufacturer	3.5	Combining percutaneous drainage and Endo-SPOINGE as a combined therapy would be counter productive, because it would not allow for an adequate vacuum to be achieved within the Endo-SPONGE device.	Thank you for your comment. The committee considered your comment carefully and acknowledged that the scenario that combined percutaneous drainage and Endo-SPONGE was not commonly used in clinical practice.
26	2	Manufacturer	3.4	These branches were based on the current Grade system available in current guidelines by ACPGBI, reports by several clinical experts within the NICE consultation process and a beneficial means of identifying number of patients who could be suitable for the different treatment options. Please add the rationale behind the four branches.	Thank you for your comment. Please see the response to comment 16.
27	2	Manufacturer	3.8	The EAC report in this supporting material has changed from the initial report submitted to the company for fact checking. The 10 year time horizon saving of scenario 1 by EAC was originally calculated at £841.23 in the original EAC report. The addition of extra tables to the current EAC report have changed the 10 year time horizon cost savings for scenario 1 and the company do not	Thank you for your comment. The committee considered your comment carefully and decided not to change the guidance. In the guidance development process there is often further work done by

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				understand how such dramatic changes have occurred (now reported as a £68.20 saving over a 10 year time horizon). In both documents for scenario 1, a cost of £1,141.10 is reported. In the original EAC report, the EAC reported that they had used the information provided in tables 5-10. Can the changes to the 10 year time horizon be explained, as until now the company have been working from the original EAC report and find changes presented to the committee by the EAC and not presented to the company as lacking in a transparency of the process. Both the EAC and the company estimated annual stoma cost at circa £3,000 per year per patient (£2896.96-£3114.5) which could be a gross underestimate as GIRFT 2017 General Surgery Report, state that the annual cost to NHS providing care in the community to an individual with a stoma of circa £6,000 per year. The economic estimates by both the EAC and company are conservative.	the EAC in preparation for the committee meeting after the company's factual check. This work forms part of the committee papers and these are shared at the consultation. After the fact checking, the EAC added 10-year time horizon modelling for all the proposed scenarios. The EAC amended mortality to be condition specific as a more accurate predictor for future costs. The amendments of the EAC report (see pages 101 to 104 of the report presenting base case results and summarising in table 13) gave more prominence to the company clinical inputs but also included the EAC clinical inputs as an alternative possibility to reflect clinical practice.
28	2	Manufacturer	4.7	While percutaneous drain and transrectal/transanal drain may be used in different circumstances, the outcomes used in the models here, refer to results from all non-surgical outcomes, this will have included these types of drains in the initial success rate submission. If placement of a transanal or transrectal drain take a different amount of time or require different number of changes the model could be adapted accordingly. The models submitted align with the expert opinion that Endo-SPONGE could reduce the need for secondary surgery compared with other non-surgical options. The primary cost saving would come from the reduction in secondary surgery rather than the direct cost of the other types of drain available. The experts discuss in the submitted material that many of them deem Endo-SPONGE could reduce the need for surgery and reduce time to stoma reversal – in line with the cost argument, even if the cost argument is not ideal. While the cost model is not ideal, there is no standard treatment for anastomotic leak nor is there any current understanding of the cost of treating anastomotic leak. Only one paper in the UK (Ashraf et al 2012) report on cost of treating anastomotic leak for 20 patients, reporting the calculated cost of anastomotic leak to be £17,220 SD±£9642. Ashraf et al report an increase in cost for anastomotic leak with conservative treatment costing £9686 ± £2626 and laparotomy costing £20671±£11,301. The small number of leaks makes generating costing data varied as small numbers are impacted by patient heterogeneity.	Thank you for your comment. The committee considered your comment carefully. It agreed there are difficulties in assessing the cost impact of Endo-SPONGE compared with other treatments because of the low patient numbers and patient heterogeneity. It amended the guidance to reflect the difficulties in comparative cost modelling with the available evidence (section 4.7). The committee considered the collection of real-world evidence would help resolve some of the difficulties (sections 4.9 and 4.10).

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				Current cost of treating anastomotic leaks are ambiguous and further clarity is unlikely due to low patient number and patient heterogeneity.	
29	3	Professional organisation		Re: NICE medical technology consultation – Endo-Sponge for treating colorectal anastomotic leakage. Comment from the Association of Coloproctology of Great Britain & Ireland ([redacted]) We would like to commend NICE on this comprehensive and well researched document regarding this relatively novel treatment. We would like to make the following comments: • The document refers to the "lack of clinical consensus about the clinical care pathway for people who have leakage after low rectal anastomosis". We would suggest that reflects the heterogeneous clinical presentation of this condition and therefore the management may be different depending on a number of different factors related to the individual, their clinical parameters and the results of relevant investigations. We would suggest that this should not influence evaluation of Endo-Sponge. 2) The evidence for cost effectiveness (summarised in section 4.7) bases this on a comparison with percutaneous drainage. We would suggest that this is not a fair comparison since this would not be an alternative treatment for a low rectal anastomotic leak with an extraperitoneal cavity, which is the clinical scenario for which Endo-Sponge would be indicated. We would suggest that a potential comparison would be more appropriately made with administration of antibiotics and a series of Examinations Under Anaesthetic. We feel it is important to also comment on the other costs for this patient group which may be influenced by use of Endosponge. These relate to: • The length of time for a patient with a defunctioning stoma. This will be the significant financial cost of stoma care as well as an emotional cost for the affected patient. b. Need for a permanent stoma. Similar costs for temporary stoma but recurring lifelong.	Thank you for your comment. The committee considered your comment carefully and acknowledged that the heterogeneous clinical presentation of anastomotic leak was discussed in relation to patient selection in clinical practice (see section 4.1). Additional work on the cost modelling examined the cost impact of using Endo-SPONGE compared with trans-anal drainage. The committee understood the need for a permanent stoma and the costs included over a 10-year time horizon were included in the model, but prolonged antibiotics use and need for recurrent examinations were not included in the model because the EAC assumed they were similar for each arm. The committee amended the guidance in section 4.7 to acknowledge the difficulties in the comparative cost modelling with the available evidence. It agreed that a register or some other real-world data collection would be valuable to assess the effectiveness of Endo-SPINGE compared with other treatment options. In section 4.10 the outcome of a feasibility assessment commissioned by NICE suggested that the optimal approach would be to establish a new national anastomotic leak registry to collect data on all patients who experience the condition, not just those receiving Endo-SPONGE

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				c. Prolonged / recurrent use of antibiotics d. Need for recurrent Examination Under Anaesthetic 3) Since there is not a clear direct alternative treatment to compare with use of Endo-Sponge in a condition with a relatively heterogenous presentation we would suggest that further randomised evaluation of this technology will be difficult and would therefore support the use of a registry to record use and allow subsequent analysis of outcome Overall we would suggest that this is a potentially useful technology which may be useful in managing a difficult clinical scenario with a heterogeneous presentation. We would suggest that recommendations regarding its use should not be based on cost evaluation alone since this is difficult to achieve given the presented information.	
30	4	Healthcare professional		The decision tree is not representative of current practice The basic premise of the EAC analysis involves a comparison with percutaneous drainage. It is apparent that this was a suggestion of the company from reading the report. It also mentions an academic grading system for leak management, which is not used in UK clinical practice to define management. I note "The Association of Surgeons of Great Britain and Ireland states that no consensus on grading system and state that ISREC is over simplistic". In looking for published guidance to inform your EAC decision tree, I note that you utilised a document written in 2016 (McDermott et al.) and note the absence of formal pathways. The entire literature in this field is weak and RCTs are rare, for obvious reasons outlined in your critique. Much relies on the expertise and experience of those involved in management – as noted in your report. To explain in more detail, patients who have a rectal anastomotic leak can usually in practice be divided into: - Those who can be treated with antibiotics and resolve (+/- diversion already in place) - Those who require drainage intervention for source control (usually with antibiotics) (+/- diversion already in place) - Those who require surgery (often septic and additional source control needed); a/ Involving laparoscopy/laparotomy, placement of drains, +/- new faecal diversion of the anastomosis prior to later reversal (potentially also utilising any of the non-operative measures for adjunctive source control as above)	Thank you for your comments. The committee considered your comment carefully and acknowledged that the current care pathway for anastomotic leaks is not clearly defined. The proposed model attempted to describe possible pathways based on experts' opinions. The committee agreed that the clinical pathway in clinical practice varies depending on patient assessment and the service availability, and this had an impact on the cost comparison. The committee amended the guidance in section 4.7 to acknowledge the difficulties in the comparative cost modelling with the available evidence. The committee considered the collection of real-world evidence could help resolve some of the difficulties (sections 4.9 and 4.10).

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				b/ Those who require laparoscopy/laparotomy, placement of drains, excision of the anastomosis and formation of an end stoma (+/- faecal diversion already in place) prior to later reversal/reconnection (potentially also utilising any of the non-operative measures for adjunctive source control as above) The design of the EAC clinical decision pathway you have reproduced will be unrecognisable to most clinicians. Clinical judgement is paramount here and a step wise approach may be taken through steps to make a decision for surgery, but occasionally the steps are not in the above order or involve multiple steps concurrently or do not involve non-surgical drainage, or revert to non-surgical drainage after surgery. The decision tree provided in the EAC document therefore does not accurately represent UK practice which is fluid, tailored and optimally responsive to the patient. This is a view supported by your experts. Why have you based your analysis and model on the EAC decision tree?	
31	4	Healthcare professional		The chosen comparator is inappropriate The comparator pathways that have been suggested are far too simplistic and the suggestion that the drainage intervention (PD or endosponge) is a comparative intervention for the same presentation, used at one time point, prior to surgery is inaccurate on many levels. Your experts are clear in this by clarifying that the indications for endosponge differ from PD: • "The clinical experts explained that, in their clinical experience, Endo SPONGE would be considered if: • the anastomotic leakage was in the low colorectal area • the leakage cavity was accessible through the anus • the leak remained localised with no abdomen or peritoneum contamination • the patient was clinically stable enough to have the procedure. The committee agreed that Endo SPONGE was indeed a 'niche' technology…" The major flaws in the choice of the comparator for this EAC analysis are: - Some leaks are treated with simple PD (once or twice intervention) and do not require an endosponge or are inappropriate for endosponge and therefore even the baseline comparison that this is a real comparator in practice is erroneous. - Endosponge in primary source control are often used for those leaks which have demonstrable anastomotic defects, are inaccessible to PD, and associated peri-anastomotic cavities which are clearly connected to, or draining into, the rectal remnant. PD is therefore not an "alternative " for endosponge for the same leak, and the same is accurate vice versa. Each technique is optimised	Thank you for your comment. Please see the response to comment 28.

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				for different reasons and based on clinical judgement and access to the technique. Indeed “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.” Furthermore, where available, endosponge may be the rescue therapy for those leaks which are not appropriate for PD, or do not resolve with PD drainage and vice versa. You have not included any of these considerations in the EAC decision tree evaluation, focusing purely on a presumed academic equipoise of primary control techniques comparing PD and Endosponge in non-operative management. This fatally undermines the entire evaluation of this technique and results in a very limited scenario evaluation of when the two techniques have equipoise for the same leak. This is a very, very rare occurrence. - The clue that this is an inappropriate comparator lies in the fact that there is not a single study comparing these techniques – simply as there is no equipoise. The report reads “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 essence, the relevant analysis here has not been performed and the appropriate evidence been not been taken into account – or at least applied in an inappropriate way.	
32	4	Healthcare professional		Endosponge may be used at many points in the surgical treatment of a leak (before or after surgery or in combination with other techniques) - The use of Endosponge is not limited to a time point prior to surgery and it use in anastomotic leak is more broadly and successfully applied often after emergency faecal diversion surgery to control sepsis and reduction in chronic sinuses/ cavities or indeed also after emergency dissection (take down) of the anastomosis, where there exists pelvic sepsis with connection to the residual rectum. - The EAC therefore ignores what is probably the more common uses of endosponge, which is also better adjunctive source control after surgery, with or without diversion. There has been no evaluation analysis of the benefit of this utilisation and it is not covered in the decision tree. Endosponge is a flexible adjunct in that management and the lack of clinical understanding in the real decision tree design in NHS practice results in a narrow / limited and flawed assessment of the device’s true potential and undermines evaluation of the broader and longer term applications of this technique.	Thank you for your comment. Please see the response to comment 30.

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33	4	Healthcare professional		Where is the comparator involving non-endosponge treated patients? - The reports states " 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, and that 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." - This is not only possible, it is the point. The clinical reality of the technology is that it provides an additional adjunct which may avoid laparotomy, anastomotic resection and/or long term stoma. It is often rescue therapy and it is simply not realistic to clinically compare it with leaks which can be rescued by PD alone. The true benefit is in its very high salvage rates in those endosponge – appropriate leaks. The comparator is therefore resultant laparotomy and downstream costs of stoma that would occur if endosponge was not used successfully and if we proceeded directly to laparotomy/ anastomotic resection without using the technology – which happens in some centres without access to the technology. The published literature provides repetitive data on success or salvage rates. - Why has NICE not undertaken comparator assessment of endosponge treated versus non-treated patients, in those patient with appropriate leaks (non-PD amenable), based on the literature?	Thank you for your comment. Please see the response to comment 28.
34	4	Healthcare professional		The expert's suggestion of using simple rectal/perianal drainage as a comparator has not been explored. - I note that the experts have suggested that PD drainage is not appropriate as a comparator and that simple rectal drainage would then become a more relevant comparator. 4.7 "Alternative comparators such as the placement of a trans-rectal or trans-anal drain may be used for leaks after a low rectal anastomosis." There has also been no attempt to evaluate the literature for simple rectal drainage as suggested by the experts. Why? - You recommend 4.7 – "A like-for-like comparison between Endo SPONGE and trans-anal and trans-rectal in people with similar clinical and anatomical characteristics is needed." On what basis do you assume the outcomes from these technologies are comparable when the literature search has not been undertaken for rectal drainage? In addition as clarified above, the decision tree supplied does not represent wider UK practice with endosponge, how will you assess this?	Thank you for your comment. The committee considered your comment carefully and acknowledged that the current care pathway for anastomotic leaks is not clearly defined which makes economic modelling challenging. Following the consultation the EAC presented additional work exploring the cost impact of using Endo-SPONE compared with trans-anal drainage as a comparator (see the addendum). The committee amended the guidance in section 4.7 to acknowledge the difficulties in the comparative cost modelling with the available evidence. It agreed that further data collection using a registry to collect all patients who had anastomotic leaks and their treatments would be valuable to improve the evidence

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				- 4.7 please expand on "The committee understood that trans-rectal and trans-anal drains are surgical alternatives for treating anastomotic leakage and that the decision problem covered all surgical techniques." What does this mean? - 4.8 "The clinical experts also added that, in their experience, endoscopy is not needed to insert Endo SPONGE, because of how close the leakage cavities are to the anal verge." How do the experts place, size the sponge, and assess the health of tissue without endoscopic assessment of the defect first? - Given the wide variation and the inappropriate comparison with PD, as outlined above and confirmed by your own experts, NICE has published : o "3.7 The cost impact of Endo-SPONGE varies depending on the scenarios and clinical parameters considered" – this paragraph should be deleted as the scenarios are not clinically relevant to the wider utilisation of endosponge and use an inappropriate comparator – and therefore this results in inappropriate analysis. - Why has NICE therefore proceeded to publish and utilise analysis of a non-comparable technologies in the public consultation document despite the experts views?	base for a comparison between Endo-SPONGE and other interventions (sections 4.9 and 4.10). The committee understood that Endo-SPONGE treatments are usually done in endoscopy units, but endoscopy is not necessarily needed to insert Endo-SPONGE. The implication of using endoscopy was considered in the cost model.
35	4	Healthcare professional	Supporting document	In appropriate time frame of economic and cost assessment model - The EAC report states "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 ". - Apart from the wrong model, this paragraph should be deleted as it is not representative of clinical practice, with an inappropriate comparator and with therefore inappropriate analysis. Has the company been given the chance to re-calculate cost savings on this recommended change? - "If treatment with PD is not as successful as with Endo-SPONGE, the cost savings will increase." This is a misnomer based on the fact that these methods are incomparable for the majority of cases	Thank you for your comment. The committee considered your comment carefully and acknowledged that the current care pathway is not clearly defined, and there were uncertainties in the clinical inputs in the cost model. The committee agreed that the scenarios that Endo-SPONGE is used combining with percutaneous drainage are not common in clinical practice.
General (comment 36 and 37)					
36	4	Healthcare professional		Available time for response The draft guidance has been available for comment for less than 1 month between the 9th of July and the 6th of August (deadline). The EAC economic evaluation of this technology runs to more than 160 pages in addition to other detailed documents supplied. As you will be aware, the majority of colorectal surgeons (the key demographic of users) are currently dealing with massive patient demand following the COVID-19 pandemic, and it is the holiday season for most individuals, meaning contact between stakeholders has been almost	Thank you for your comment. The committee considered your comment carefully and acknowledged that NICE followed its standard process when the guidance development was resumed after the COVID-19 pandemic. It was a challenging time for everyone, particularly those working in the health service and so we appreciate your contribution to the

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				impossible. Expecting robust end user and public evaluation of the draft guidance documents is entirely unreasonable given the circumstances and time scales available. Given that feedback is inappropriately rushed during this period of high volume and intensity for colorectal surgeons, I would suggest that your aim for stakeholder engagement may be unmet (I would expect that this may be apparent in the lack of engagement or responses received). However, I am grateful that you have graciously permitted me an additional 3 business days beyond the published deadline, when informed of the above difficulties with submission and that this timescale was not appropriate. I note that you maintained the closure deadline for submissions online unchanged. Clearly, a lack of stakeholder engagement will undermine the process adding to what is an already questionable assessment with several major flaws.	consultation. In addition, the ACPGBI also contributed to the consultation and the feasibility report improved the stakeholder engagement for this topic. NICE is reviewing its methods and processes for guidance development to improve stakeholder engagement and to ensure the guidance development process in the future is more agile and able to adapt to unexpected situations.
37	4	Healthcare professional		Can I apologise for the unpolished document above but time has not been forthcoming to rephrase things as ideally as I would wish given the imminent deadline. However, can I say from the outset that I am alarmed at the processes observed and undertaken in relation to the NICE evaluation of this technology. I am a high volume user of endosponge and as a declaration of interest I have spoken at courses for the company involved, provided consultancy and have been in contact with them with concerns over this evaluation. It is apparent that the company have made several errors in understanding that have found their way through to the EAC. The NICE evaluation should not propagate these errors. I note 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. Another 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. Your own analysis states “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 a physician I am very worried that the flawed analysis will concern patients and surgeons and will result in a negative effect and confidence on the use of this technology. None of that negative effect I feel is in fact justified when looking at the safety profile, salvage rates gained, and literature available, in an environment which is very badly researched. My suggestion is that NICE starts again, defining the pathways correctly, choosing the right comparator and providing the best pragmatic advice to	Thank you for your comment. The committee considered your comment carefully and acknowledged that Endo SPONGE is a 'niche' technology that could be considered for a relatively small number of patients. It agreed that Endo-SPONGE has potential for treating people with anastomotic leaks but the evidence base is weak because of the small population and the fact that there is no clearly defined care pathway for treating anastomotic leaks. Therefore, the committee concluded that further research using real-world data would be valuable to assess the effectiveness of Endo-SPONGE compared with other treatment options. This recommendation is not intended to deter the use of the technology within the NHS. The guidance overview states that: ‘If the technology is recommended for use in research, the recommendations are not intended to preclude the use of the technology in the NHS but to identify further evidence which, after evaluation, could support a recommendation for wider adoption.’

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				clinicians about the use of this technology. The current evaluation is not robust, useful and has many flaws. It is not realistic advice and I worry about it remaining published in its current format.	

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