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Medical technology consultation: Endocuff Vision for assisting visualisation during colonoscopy

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.

Title: Endocuff Vision for Endoscopic Investigation

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Declared interests of the authors

Description of any pecuniary relationship with the company, both personal and of the EAC. Please refer to NICE's Code of Practice for declaring and dealing with conflicts of interests.
http://www.nice.org.uk/niceMedia/pdf/Guidanceondeclarationsofinterest.pdf

None

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Rider on 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
ADR	Adenoma detection rate
BCSP	Bowel Cancer Screening Programme
CI	Confidence interval
CRC	Colorectal cancer
DH	Department of Health
EAC	External Assessment Centre
EV	Endocuff Vision
EVC	Endocuff Vision colonoscopy
FOBT	Faecal Occult Blood Test
FIT	Faecal immunochemical test
IQR	Interquartile range
ITT	Intention to treat
MAUDE	Manufacturer and User Facility Device Experience
MAP	Mean adenoma per patient
MHRA	Medicines & Healthcare products Regulatory Agency
MPP	Mean polyps per patient
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
PDR	Polyp detection rate
PP	Per protocol
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic sensitivity analysis
QUORUM	Quality of Reporting of Meta-analyses
RCT	Randomised Controlled Trial
SC	Standard colonoscopy
SD	Standard deviation
VAS	Visual Analogue Scale
vs	Versus

1 Executive Summary

The sponsor included in their submission 4 clinical studies (3 published in full text and 1 as a conference abstract). Two of the included studies were RCTs (ADENOMA, E-Cap) and 2 non-RCTs (Rameshshanker 2016, Tsiamoulos 2018). The EAC did not identify any further relevant evidence.

The pivotal study is the multi-centre, single-blind, national ADENOMA (n = 1772) RCT, which compared EVC with standard colonoscopy with a 21 days follow-up (Ngu 2018) in adults referred for colonoscopy following either clinical symptoms, post-polypectomy surveillance or FOBt-positive as part of the BCSP. The results reported a statistically significant increase in ADR for the whole population, in favour of EVC (from 36.2% to 40.9%, p=0.02). The subgroup analysis showed that the increase was driven by a 10.8% increase in the FOBt-positive screening population (61.7% EVC vs 50.9% SC, p<0.001). The secondary outcomes of MAP and PDR were also statistically significant higher in favour of the EVC group. The EAC considered that this multi-centre RCT, which included only UK sites, was subject to overall low risk of bias and the comparative benefit was mainly attributable to EVC.

As noted in the national BCSP audit (Lee 2012), there is considerable variation in ADR between colonoscopists, ranging from 21.9% to 59.8%. As the audit reports a mean baseline ADR of 46.5%, an ADR above that can be considered as high. Given the association between a colonoscopist's expertise and ADR (higher expertise resulting in higher baseline ADR), and the evidence supporting the notion that the effect of EVC (E-Cap, Tsiamoulos 2018, observed with the older Endocuff version as well (Willet 2018) is dependent on the colonoscopist's expertise, it is likely that EVC will not lead in an increase in ADR in centres with high expertise and high baseline ADR rates.

The manufacturer's cost model indicated a potential saving of £12 per patient in the BCSP over a period of ten years. The savings arise from averted CRC and CRC diagnosed at an earlier stage through improvements in the ADR of colonoscopy with EVC. The EAC reviewed the cost analysis and considered it to be appropriate. The EAC noted that cost savings are sensitive to the increase in ADR with EVC. An increase of 8.35% was required for EVC to be cost neutral in the BCSP. The manufacturer's analysis was consistent with the limited evidence on the cost-effectiveness of EVC in the literature.

2 Background

2.1 Overview and critique of company's description of clinical context

The sponsor provided a brief overview of the clinical context and prevalence of colorectal adenomas and colorectal cancer. The clinical context provided by the sponsor is considered appropriate. The sponsor presented the current pathway for endoscopic investigation in people undergoing colonoscopy for suspected bowel cancer, for the removal of known polyps and for surveillance following previous adenoma removal in figure A4 of their submission (please see Figure 1 below). According with the existing pathway, the following patient populations may be referred for colonoscopy:

- people with symptoms suggestive of colorectal cancer
- people from the bowel cancer screening programme with a positive FOBT
- people on surveillance after removal of adenomatous polyps or for inflammatory bowel disease
- screening in people with familial adenomatous polyposis, Lynch syndrome, a significant family history or other risk factors

Apart of the addition of Endocuff Vision during colonoscopy no further changes to the pathway are proposed. The sponsor's submission also provided a brief description of the main national guidelines on colonoscopic screening and surveillance and these are summarized below.

For people aged 55-60 years, flexible sigmoidoscopy screening is being rolled out (Public Health England 2015). For people aged 60 to 74, the NHS BCSP recommends offering bowel cancer screening every 2 years. This screening currently involves a faecal occult blood sampling test. Those people with abnormal results should be offered to undergo a colonoscopy.

NICE's guideline on suspected cancer recommends that people with suspected CRC should be referred within two weeks. The symptom severity for referral varies according to age from people aged 40 and over presenting with unexplained weight loss and abdominal pain to people aged 60 and over presenting with iron-deficiency anaemia or changes in their bowel habit. Similar to the NHS Bowel Cancer Screening Programme instructions any patient testing positive for occult blood in their faeces should be referred.

For symptomatic patients, NICE diagnostics guidance on quantitative faecal immunochemical tests to guide referral for colorectal cancer in primary care

recommends the use of 3 FITs. These tests are recommended for guiding referral in people without rectal bleeding, who do not meet the criteria for a suspected cancer referral outlined in NICE's guideline on suspected cancer. Other investigative tests, such as a barium enema or a flexible sigmoidoscopy, may also be conducted. A positive investigative test should be followed by a biopsy for diagnostic proof and staging is performed using contrast-enhanced CT.

NICE's clinical guideline on colorectal cancer prevention: colonoscopic surveillance in adults with ulcerative colitis, Crohn's disease or adenomas, recommends colonoscopic surveillance for people with adenomas. The frequency of colonoscopy depends on the risk of developing colorectal cancer (low, intermediate or high) that is determined by the size and number of adenomas with more and bigger adenomas representing a higher risk. People with low risk should undergo colonoscopy every 5 years, with intermediate risk every 3 years and annually with those at high risk.

The NICE guideline on colorectal cancer: diagnosis and management recommends that people with suspected CRC without major comorbidities should undergo colonoscopy to confirm their diagnosis. Everyone treated for CRC should also undergo surveillance colonoscopies at 1 year post curative resection and, if normal, should have this repeated at 5 years. Similar recommendations, albeit focused on people with intermediate or high risk for CRC, are provided by the British Society of Gastroenterology (BSG) and the Association of Coloproctology for Great Britain and Ireland (ACPGBI) guidelines for colorectal cancer screening and surveillance (Cairns et al. 2010).

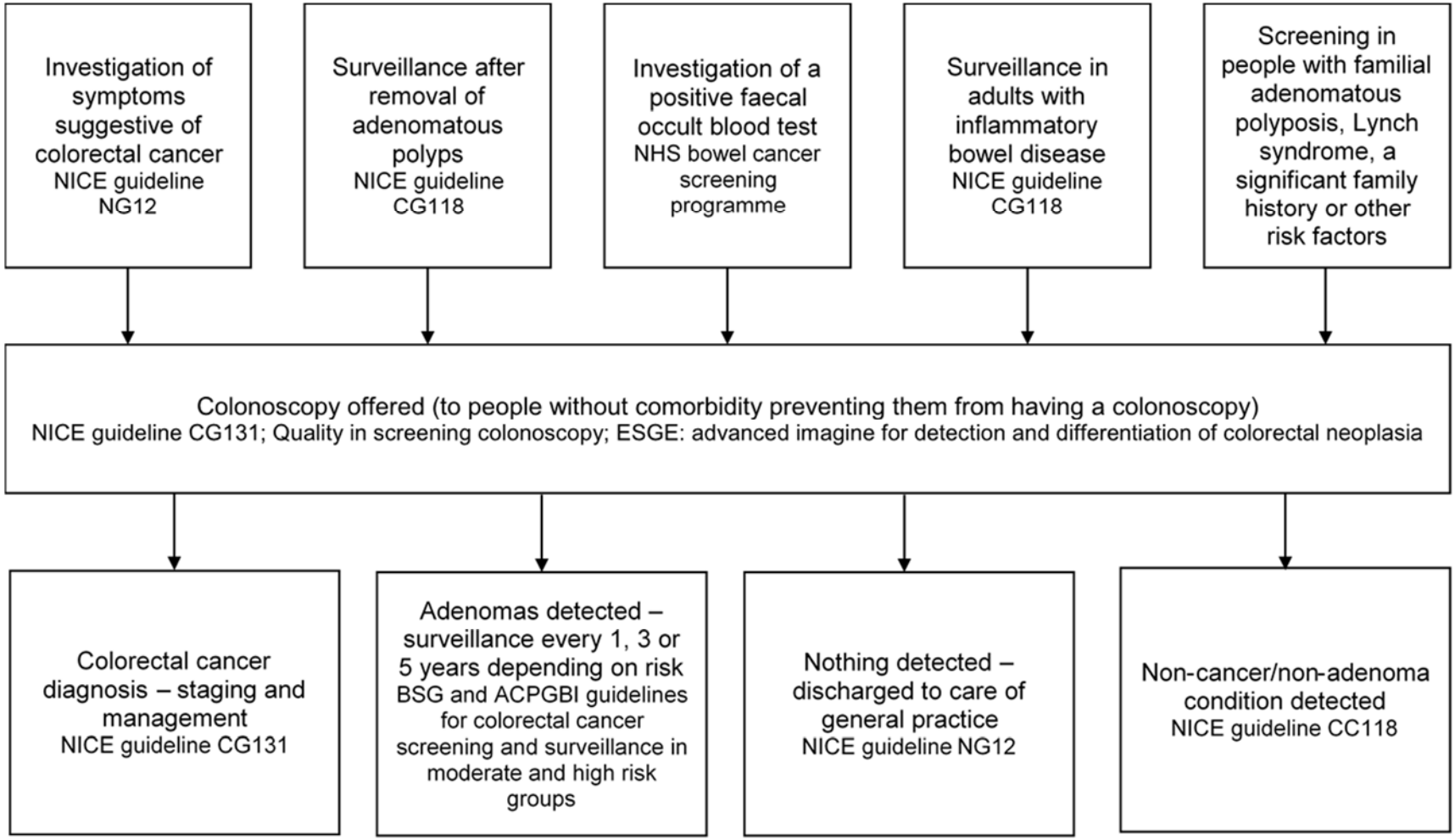


Figure 1: Overview of care pathway as included in the sponsor's submission.

2.2 Critique of company's definition of the decision problem

Table 1 below outlines the main issues with the company's definition of the decision problem based on the original scope.

Table 1: Critique of decision problem

Decision problem	Company submission	Matches decision problem? (Y/N/partially)	EAC comment
Population	Scope: “People undergoing colonoscopy for suspected bowel cancer, for the removal of known polyps and for surveillance following previous adenoma removal.” Submission: Three of the submitted studies 1 RCT (E-Cap) and 2 non-RCTs (Rameshshanker 2016, Tsiamoulos 2018) involved people attending for screening colonoscopies. In addition, the E-Cap RCT also included people for surveillance after removal of polyps. One RCT (ADENOMA) involved a more heterogeneous population, specifically people referred for colonoscopy for clinical symptoms, as part of a post-polypectomy surveillance programme or with positive FOBt as part of the BCSP (Ngu 2018).	Yes	All of the evidence submitted meets the final scope for the population. All studies included an adult population, however, the ADENOMA RCT (Ngu 2018) included patients >18 years old whilst the other 3 studies included older patients (>55 years old) more typical of a CRC screening population. ADR increases with age. With the exception of Rameshshanker 2016 that did not report men to women ratio, all other studies included a higher proportion of men rather than women. The ADR is higher in men than women.

	All included studies analysed an adult population and were conducted in a UK setting.		
Intervention	Scope: “Colonoscopy with the addition of an Endocuff Vision device.” Submission: All 4 included studies (ADENOMA, E-Cap, Rameshshanker 2016, Tsiamoulos 2018) used standard colonoscopy with Endocuff vision.	Yes	All included evidence used EVC without, however, specifying the exact size which according to the manufacturer varies depend upon the colonoscope used. The 4 sizes and associated colour coding available are: • Purple (lumen/inner diameter: 10.4mm) • Blue (lumen/inner diameter: 11mm) • Green (lumen/inner diameter: 11.2mm) • Orange (lumen/inner diameter: 12.1mm) The sponsor has published a compatibility list with all currently available endoscopes on their website. A copy of the most recent updated list is included in appendix C of the report. The sponsor provided proof of CE marking compliance according with the Medical Device Regulation.
Comparator(s)	Scope: “Colonoscopy” Submission: The sponsor submitted 4 comparative studies, 2 RCTS and 2 non-RCTs studies. All studies compared EVC with standard colonoscopy.	Yes	Comparative evidence from 2 RCTs and 2 non-RCTs were included in the final report. The types of scopes used in each study are listed below: • ADENOMA RCT: Olympus colonoscopes were used in 1760/1772 cases and there was no difference in type of scope found between both study arms • E-Cap: Olympus colonoscopes were used in both arms (Olympus Spectrum CV260SL

			processor, Olympus CF-H260 endoscopes, CO2, and Olympus scope guide, Tokyo, Japan) • Rameshshanker 2016: No information provided • Tsiamoulos 2018: Olympus colonoscopes were used According to information received from the Joint Advisory Group on GI Endoscopy, almost all endoscopies in the UK are carried out using Olympus, Pentax or Fuji equipment.
Outcomes	Scope: "The outcome measures to consider include: – Procedural outcomes – Mean number of adenomas detected per procedure (MAP) – Adenoma detection rate (ADR) overall and ADR by location in the colon (right or left) – Type of polyp (e.g. Sessile serrated polyp) – Size of polyp (diminutive, small and large) – Overall procedure time (time to caecal intubation, time to withdrawal, training time on using Endocuff Vision®)	Partially	In the sponsor submission outcomes are tabulated by study (table B14 to B29). Outcomes from 2 RCTs and 2 non-RCTs are presented in 4 references (3 full texts and 1 conference abstract). Only the ADENOMA RCT was adequately powered to detect a difference in ADR. The E-Cap RCT was powered to detect a difference in MPP. There is currently no strong evidence to support an association between MPP and a reduction in CRC. None of the studies was adequately powered to detect a difference in secondary outcomes. ADR is dependent on colonoscopist's expertise, therefore, evidence from single-centre studies are not considered representative of UK practice as a whole. The ADENOMA RCT is the only multi-centre study.

	– Caecal intubation rates – Number of repeat colonoscopies and sub-optimal examinations – Polyp distribution in different parts of the colon – Cancer diagnosis and management: o Rate of diagnosis of bowel cancer o Referral rates for specialist treatment and rates of subsequent surgery, chemotherapy and radiotherapy o Tumour recurrence after colonoscopic resection o Rate of repeat colonoscopy after electrocoagulation for angiodysplasia – Patient outcomes: o Patient comfort and experience o Device-related adverse events for example complication rate (mucosal lacerations or major bleeding, perforation		

	or loss of Endocuff Vision®)'' Details on outcomes are given by study submitted in tables B9 (published) and B10 (unpublished).		
Cost analysis	Scope: ''Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be sufficiently long to reflect any 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.''	Yes	The cost analysis submitted by the sponsor matches the cost analysis specified in the final scope. The model is appropriate to capture the costs and consequences of the technology compared to the specified comparator.
Subgroups	Scope: '' People referred for colonoscopy through the NHS bowel cancer screening programme. People offered colonoscopic surveillance because they have had adenomas removed. People offered colonoscopy after reporting symptoms to a general practitioner.'' Submission: Three of the submitted studies 1 RCT (E-Cap) and 2 non-RCTs	Yes	The ADENOMA RCT subgroup analysis shows that the ADR increase in the EVC is driven by an increase in the FOBt-positive screening population.

	(Rameshshanker 2016, Tsiamoulos 2018) involved people attending for screening colonoscopies. One RCT (ADENOMA) involved a more heterogeneous population, specifically people referred for colonoscopy for clinical symptoms, as part of a post-polypectomy surveillance programme or with positive FOBt as part of BCSP (Ngu 2018). The results were reported in combination and for each subgroup separately.		

Special considerations, including issues related to equality

In their submission the sponsor noted that Endocuff Vision should not be used in people who cannot have colonoscopies, including those with colonic strictures, known diverticular disease and known acute colitis (see section 6). The final scope also notes that Endocuff Vision cannot be used for small bowel investigations. The prevalence of diverticular disease increases with age and age is a protected characteristics under the 2010 Equality Act.

The EAC has not identified equality issues other than those highlighted in the scope.

3 Clinical evidence

3.1 Critique of and revisions to the company's search strategy

The EAC considered the sponsor's search to be adequate and well reported, with a thorough number and variety of sources searched. However, the final search was undertaken in February 2018 (encompassing records from 2010 onwards) so the EAC decided to re-run the search in order to cover the period up to July 2018.

The search carried out by the sponsor was re-run with the following alterations: NHS EED and DARE were not searched (these databases were closed to new records in 2015); EconLit was searched via the Proquest platform (as opposed to Ovid SP) - the operator syntax was translated but there were no other changes made to the search; the EAC did not do a search for abstracts of the American College of Gastroenterology Annual Scientific Meeting and the United European Gastroenterology Week because neither meeting has taken place yet (as of the 5th of July) in 2018; finally, all searches were date-limited to 2018 and duplicates from the original search manually removed.

There were 474 records retrieved and 313 following de-duplication in EndNote. No further additional studies were included based on this search.

3.2 Critique of the company's study selection

The sponsor's inclusion/exclusion criteria are listed in Table 2 below.

Table 2: Sponsor's inclusion/exclusion criteria for study selection

Inclusion criteria	
Population	Studies of adult (over 18 years of age) patients scheduled for colon screening, colonic surveillance or diagnostic colonoscopy, for any reason.

Inclusion criteria	
Interventions	Studies that evaluate ENDOCUFF VISION® –assisted colonoscopies.
Comparators	Standard colonoscopies (i.e. colonoscopies with no distal device attached).
Outcomes	Studies that report data on one or more of the following clinical or safety outcomes: • Detection rate: o Benign polyps (types, location); o Adenoma (ADR) (types, location, definition used at each stage); o Cancers. • Device insertion and withdrawal time; • Duration of colonoscopy; • Caecal intubation rate (CIT); • Mean number of adenomas per patient (MAP); • Miss rate (where recorded); • Outcomes relating to patients' comfort and satisfaction; • Complications, including: o Removal of device due to patient issues; o Device retrieval if detached from scope. • Adverse events, including: o Bowel perforation; o Mucosal petechiae/ scratches; o Anal discomfort. • Long term outcomes (Protocol Amendment (PA)1[1]) o Incidence of subsequent interval cancers; o Referral rates for specialist treatment and rates of subsequent surgery, chemotherapy and radiotherapy; o Tumour recurrence after colonoscopic resection; o Rate of repeat colonoscopy after electrocoagulation for angiodysplasia.
Study design	• Randomised controlled trials (RCTs) of any size and duration; • Non-randomised comparative and uncontrolled studies, which report relevant clinical effectiveness or safety data for ENDOCUFF VISION®; • Non comparative or single arm studies, which provide relevant safety data; • Studies published as abstracts or conference presentations will be eligible if adequate data are provided; • Systematic reviews as a source of references to relevant primary studies.
Language restrictions	• No language limits (although studies reported in languages other than English would not be extracted, but would be listed for information only).
Search dates	• 2010 to the current date.
Exclusion criteria	
Population	Studies of patients under the age of 18 years or of adult patients who are not scheduled for colon screening, colon surveillance or diagnostic colonoscopy for reason.

[1] PA1- additional outcomes following receipt of the NICE draft scope.

Inclusion criteria	
Interventions	Studies that do not evaluate ENDOCUFF VISION®–assisted colonoscopies.
Outcomes	Studies that do not report data on one or more of the outcomes listed in the inclusion criteria.
Study design	Any study design that is not listed in the inclusion criteria.
Language restrictions	N/A
Search dates	

The EAC considered the inclusion/exclusion criteria to be appropriate. After sifting 3,497 records and reading 122 full text publications, the sponsor identified a total of 19 references reporting on the results of 4 studies. The sponsor provided a justification for excluding the rest of the 103 full text publications the majority of which (73) were due to using an ineligible intervention/comparator. The EAC requested and received a list of these 103 full text publication and the reasons for exclusion were re-reviewed. There was agreement between the EAC's and the sponsor's decision for exclusion for these publications. Three of the 4 included studies had several related conference abstracts. However, as they reported on overlapping populations and they reported interim results, only the results included in the full text publication were considered in the submission. For one study (Rameshshanker 2016) results were only available in 1 conference abstract. All studies included by the sponsor fit the scope.

3.3 Included and excluded studies

Table 3: List of included studies identified by the sponsor and the EAC

Primary study number	Primary study reference	Study name	Sponsor inclusion	EAC inclusion	Reason for disagreement
1.	ADENOMA	Ngu 2018	Yes	Yes	N/A
2.	E-Cap	Bhattacharyya 2017	Yes	Yes	N/A
3.	N/A	Tsiamoulos 2018	Yes	Yes	N/A
4.	N/A	Rameshshanker 2016	Yes	Yes	N/A

Included studies

The EAC included the following studies:

RCTs

Full text publications

Ngu (2018) – ADENOMA – ClinicalTrials.gov number NCT02552017

This single-blind RCT compared EVC with standard colonoscopy in 1772 adults referred for colonoscopy following either clinical symptoms, post-polypectomy surveillance or FOBt-positive as a part of the BCSP. Patients were randomised 1:1 and were seen at 6 hospitals in the north east of England and in 1 hospital in London. All colonoscopists were required to perform at least 20 colonoscopies before participating in the trial, with a maximum of 10 colonoscopists per site of which a maximum of 4 were BCSP-accredited. The primary endpoint was adenoma detection rate (ADR). Patient characteristics and bowel preparation standards were not significantly different between the groups. ADR was significantly higher in the EVC compared to the standard colonoscopy group, under intention-to-treat analysis (40.9% vs. 36.2%, p=0.02). This result was consistent with the per-protocol analysis (As no patients were lost to follow-up, the ITT and PP populations are identical). In subgroup analyses only in BCSP-referred patients was there a significant difference in ADR between the groups (61.7% vs. 50.9%, p=0.001). For the secondary endpoints the results followed a similar pattern with overall significant differences between the groups, in favour of the EVC group, driven by significant differences in BCSP-referred patients but not the non-BCSP patients. Polyp cancer detection rate was significantly higher in the EVC group but only in the BCSP subgroup (0.8% vs. 0%, p=0.04). By contrast, for sessile serrated adenomas there was a

significant difference in favour of EVC but in this case driven by the non-BCSP patients (2.3% vs. 1.1%, p=0.03). Caecal intubation rates were equivalent in both groups, with no differences in withdrawal times in cases without polyps. Hyoscine-n-butylbromide to relax the colon was used in significantly more cases in the EVC group (627 vs. 568, p=0.002), though there were no significant differences in carbon dioxide or air insufflation.

Critical appraisal:

The intervention was blinded only to the pathologist, not to the patient or endoscopist, though there are no other concerns relating to selection bias. It should be noted that due to the nature of the intervention double blinding design is difficult to implement. Only one of the 47 endoscopists significantly increased ADR during the course of the study, which suggests there are minimal concerns about performance bias. The EAC noted the unusual way in which the learning curve was reported whereby there were no differences in ADR "between the first 20% and last 20% of procedures". The authors intended for the study to recruit around 20% of the patients from BCSP referrals, though ultimately 44.4-45.6% were recruited via this route. The study was powered to detect a 6% increase in ADR (at a beta of 90% and an alpha of 0.05). The study was powered as a superiority trial and one-sided t-tests were used for the primary endpoint. Therefore, the upper bound of the 95% confidence intervals are reported as infinity. There was a very high number of patients deemed ineligible, who declined to participate or who were otherwise unable to be randomised (2156 of 3928 patients, 54.9%), but there were otherwise no concerns about attrition bias. Other aspects of the study are methodologically strong and an independent organisation was in charge of the randomisation procedure and data analysis. The study recruited participants from 7 UK centres. The study was funded by the National Institute for Health Research (NIHR).

Bhattacharyya (2017) – E-cap – ClinicalTrials.gov number NCT02529007

534 adult patients were randomised and 531 were analysed 1:1 in a single-blind RCT comparing EVC to standard colonoscopy. Patients were recruited from the BCSP following FOBt-positive (either index colonoscopy or post-polypectomy surveillance) and treated in a single centre in the UK. All endoscopists were BCSP-accredited (minimum lifetime experience of 1000 colonoscopies, plus other performance criteria) and performed at least 15 colonoscopies with EV before the beginning of the trial. The primary endpoint was mean polyps per patient (MPP). Baseline characteristics were similar between the groups except for male-female ratio, which was 1.8:1 overall, and withdrawal time, which was significantly shorter in the EVC group (16.9 vs. 19.5 minutes, p<0.005). There were no significant differences between the groups in MPP, adenomas, mean adenomas per patient, polyp detection rate,

ADR, proximal polyps or adenomas, advanced ADR, or cancer detection rate. Among participating endoscopists the ADRs did not differ significantly during the study compared to the 6 months prior to the study. With the exception of withdrawal time, subgroup analysis in patients with a positive FOBt revealed no significant advantage to EV.

Critical appraisal:

In this study the intervention was blinded to the patient but not the endoscopist. The groups were not well matched in male-female ratio (1.8:1), though there were no other concerns surrounding selection or performance bias. The study was powered to detect a 30% difference in MPP (at a beta of 80% and an alpha of 0.05), assuming an average of 1.6 polyps detected per patient and an SD of 2.05. There are no concerns surrounding attrition bias. The authors contend that MPP is a more appropriate outcome measure than ADR (which is the outcome measure used in other studies) and there are no other concerns surrounding detection bias. However, MPP includes polyps with no malignant potential in its reporting and therefore may not translate adequately to a relevant reduction in interval cancers like ADR. This is a single-centre study. ADR rates reported from single-centre studies will be biased by the level of local expertise. Therefore, this study is at high risk for this source of bias and therefore not representative of UK practice as a whole. Other aspects of the study are methodologically strong and an independent organisation was in charge of the randomisation procedure and data analysis. The study recruited participants from a UK centre. The study was funded by the National Institute for Health Research (NIHR).

Non-randomised RCTs

Full-text publications

Tsiamoulos (2018)

This study is a pilot service evaluation of EV, setup up as a before-after study in 410 adult patients recruited from the BCSP with a positive FOBt and treated in a single centre in the UK. In total there were 137 colonoscopies performed before and without (“pre-cuff”), 136 with (“cuff”), and 137 after and without (“post-cuff”) the EV device. All endoscopists were BCSP-accredited (>5000 procedures each) and 3 of the 4 had no experience of using EV previously. Baseline characteristics were comparable between the 3 groups. Overall, ADR was significantly increased between the pre-cuff and cuff periods (16% increase, $p<0.03$), though there were no significant differences when each endoscopist was analysed separately. There were no significant differences between the cuff and post-cuff or pre-cuff and post-cuff periods. One endoscopist increased ADR in the post-cuff compared to the cuff period.

Mean adenomas per procedure (MAP) was significantly increased between the pre-cuff and cuff periods (83% increase, p=0.007), but there were no significant differences between other periods. Caecal intubation time was significantly increased in the pre-cuff compared to the cuff periods (1 minute longer, p=0.002) and significantly increased in the post-cuff compared to the cuff period (2 minutes longer, p=0.002), although there were no significant differences between the pre-cuff and post-cuff periods. Similarly, negative colonoscopy time was significantly longer in the pre-cuff compared to the cuff period (12 vs. 8.5 minutes, p<0.001) and significantly longer in the post-cuff compared to the cuff periods (9.75 vs. 8.5 minutes, p=0.05). Midazolam use was statistically significant lower in the cuff period compared to the pre-cuff and post-cuff periods but fentanyl use and comfort scores were not significantly different between the groups. In the cuff period there were 8 failed cases in which the device had to be removed in order to complete the colonoscopy (6 due to severe diverticular disease, 2 due to anal discomfort on insertion). In the pre-cuff and post-cuff periods there 8 and 2 failed cases, respectively, all due to difficulties in sigmoid colon negotiation.

Critical appraisal:

This study is presented as a service evaluation study and data were collected prospectively for the cuff and post-cuff periods, but retrospectively for the pre-cuff period. Failed colonoscopies (unsuccessful caecal intubation) were excluded from the analysis and there is no evidence that intention-to-treat analyses were performed. Bonferroni correction was employed to adjust for multiple comparisons. There are few concerns surrounding attrition bias and the authors discuss reasons why the post-cuff period was not significantly different to the cuff period in terms of ADR and MAP. The endoscopists were very experienced (>5000 previous cases performed each) which may limit the generalisability of these outcomes to general UK practice. This is a single-centre study. ADR rates reported from single-centre studies will be biased by the level of local expertise and the prevalence of underlying risk factors in the local population. Therefore, this study is at high risk for this source of bias and therefore not representative of UK practice as a whole.

Non-RCTs

Abstracts

Rameshshanker (2016)

This study prospectively compared EVC with standard colonoscopy in 96 consecutive adult patients in a single centre in the UK. Colonoscopies were carried out by a single experienced endoscopist. 49 patients had EVC and 47 had SC. The outcome measure used was the SP6, which is the

number of pre-cancerous lesions (adenomas *and* sessile serrated polyps) per 6 minutes of withdrawal time. Caecal intubation and withdrawal times were not significantly different between the groups. However, ADR (83.67% vs. 55.32%, p=0.004) and SP6 (1.11 vs. 0.6, p=-0.0004) were both significantly increased in the EVC group compared to standard colonoscopy.

Critical appraisal:

This study is published as a conference abstract and does not report many important variables, such as baseline demographics, recruitment protocols or how interventions were allocated. EVC was used at the discretion of the endoscopist. The SP6 outcome measure is not used elsewhere in the literature though it is posited as a better performance measure than ADR. However, the authors do also report ADR. This is a single-centre study. ADR rates reported from single-centre studies will be biased by the level of local expertise. Therefore, this study is at high risk for this source of bias and therefore not representative of UK practice as a whole.

Table 4 and Table 5 below provide detailed information on the patient and procedure characteristics and methodology for each of the included studies.

Table 4: Patient characteristics of included studies

Characteristic	ADENOMA	E-Cap	Tsiamoulos 2018	Rameshshanker 2016
Age mean (SD) or median (IQR)	EVC: 61.7 (11.7) SC: 62.1 (11.1)	EVC: 68 (63-70) SC: 67 (64-71)	EVC: 65 (62-70) SC: 67 (61-71)	65 (55–74)
Age <60 years	EVC: 273 (30.7%) SC: 273 (30.9%)	EVC: 266 (100%) SC: 265 (100%)	100%*	NR
Male	EVC: 507 (57.1%) SC: 502 (56.8%)	EVC: 162 (60.9) SC: 180 (67.9)	EVC: 76 (55.9) SC: Pre-cuff: 81 (59.1) Post-cuff: 73 (53.3)	NR
Previous abdominal surgery	EVC: 341 (38.4%) SC: 342 (38.7%)	NR	NR	NR
Recruitment	EVC: Non-BCSP patients: 494 (55.6) BCSP patients: 394 (44.4) SC: Non-BCSP patients: 481 (54.4) BCSP patients: 403 (45.6)	BCSP: 100%	BCSP: 100%	BCSP: 100%
Indication for colonoscopy:				
i) BCSP	EVC: 274 (30.9%) SC: 282 (32%)		BCSP: 100%	BCSP: 100%
ii) BCSP surveillance	EVC: 89 (10%) SC: 88 (10%)			

iii)	Colonoscopy conversion from bowel scope	EVC: 31 (3.5%) SC: 32 (3.6%)			
iv)	Symptomatic diagnostic	EVC: 357 (40.2%) SC: 346 (39.1%)			
v)	Symptomatic surveillance	EVC: 137 (15.4%) SC: 135 (15.3%)			
vi)	Positive FOBT		EVC: 188 (70.7) SC: 183 (69.1)		
vii)	Polyp surveillance		EVC: 78 (29.3) SC: 82 (30.9)		
*Based on the paper reporting that they recruited people from the NHS bowel cancer screening programme					

Table 5: Procedure characteristics of included studies

Characteristic	ADENOMA	E-Cap	Tsiamoulos 2018	Rameshshanker 2016
Good/adequate bowel prep	The authors stated that bowel preparation was of an equivalent standard in both groups	EVC: 260 (97.7%) SC: 259 (97.7%)	NR	NR
Use of hyoscine-n-butylbromide	**EVC:** 627 (70.6) BCSP: 300 (76.1) Non-BCSP: 327 (66.2) **SC:** 568 (64.3) BCSP: 309 (76.7) Non-BCSP: 259 (53.9)	NR	NR	NR
Use of carbon dioxide gas	**EVC:** 672 (75.7) BCSP: 357 (90.6) Non-BCSP: 315 (63.8) **SC:** 678 (76.7) BCSP: 367 (91.1) Non-BCSP: 311 (64.7)	NR	NR	NR
Use of Midazolam	NR	NR	EVC: 0.86mg SC: 0.99 - 1.03 mg	NR
Use of Fentanyl	NR	NR	EVC: 33mcg SC: 34 - 36mcg	NR
Position change	**EVC:** 718 (81.3) BCSP: 326 (83.2) Non-BCSP: 392 (79.8) **SC:** 772 (87.5)	NR	NR	NR

	BCSP: 359 (89.3) Non-BCSP: 413 (86.0)			
Rectal retroflexion	**EVC:** All pts: 723 (81.4) BCSP: 322 (81.7) Non-BCSP: 401 (81.2) **SC:** 785 (88.8) BCSP: 363 (90.1) Non-BCSP: 422 (87.7)	NR	NR	NR
Caecal intubation time (IQR)	**EVC:** 8 (5-12) BCSP: 7 (4-10) Non-BCSP: 10 (7-14) **SC:** 9 (6-15) BCSP: 6 (4-11) Non-BCSP: 12 (8-17)	EVC: 15.75 SC: 15.89	EVC: 7 **SC:** Pre-cuff: 8 Post-cuff: 9	NR
Withdrawal time (IQR)	**EVC:** 8 (6-10) BCSP: 8 (6-10) Non-BCSP: 7 (5-10) **SC:** 8 (6-11) BCSP: 9 (7-12) Non-BCSP: 7 (5-10)	EVC: 16.9 SC: 19.5	EVC: 8.5 **SC:** Pre-cuff: 12 Post-cuff: 9.75	NR
Adverse events	EV: 11 Standard: 12	NR	**Anal discomfort:** EV: 2 (1.5%) Standard: NR	NR
Comfort	Regarding discomfort on anal intubation, 8.6% patients found EV more uncomfortable; however, for	**Comfort Score:** EV: 1.57 standard: 1.46 p=0.27	EV was electively removed from 2 patients due to	NR

	all other measures of comfort EVC was non-inferior.		discomfort during intubation.	

Table 6: Methodological characteristics of included studies

Included reference	Design and intervention(s)	Participants and setting	Outcomes	Withdrawals	EAC Comments
Ngu 2018 (ADENOMA trial)	Prospective, single blind, two-arm, multicentre randomised control trial with 21 days follow up. UK Endocuff Vision-assisted (EVC) or standard colonoscopy (control)	1772 adult patients (outpatients) referred for colonoscopy for • clinical symptoms • as part of a post-polypectomy surveillance programme • with positive FOBt as part of BCSP EVC = 888 Colonoscopy = 884	Adenoma detection rate (ADR) *(primary outcome)* Mean adenomas per procedure Polyp detection rate Sessile serrated adenomas Left colon adenomas Right colon adenomas Large adenomas (10+mm) Small adenomas (6-9mm) Diminutive adenomas (≤5mm)	All but one patient from the EVC group completed treatment. No patients were lost to follow-up.	Overall, good methodological quality. Only the pathologist was blinded to the use of EV. Superiority of EVC effect compared with standard colonoscopy was concluded (p=0.02) based on an ADR increase by 4.7%, mainly attributed to the screening cohort.

			Cancer detection rate (all cancers) ●		
Bhattacharyya 2017 (E-cap trial)	Prospective, single-blind, two-arm, single centre randomised control trial, UK ● Endocuff Vision-assisted (EVC) or standard colonoscopy (control) ●	534 adult patients (59-75 years) referred for BCSP colonoscopy with positive FOBT EVC = 266 Standard colonoscopy = 265 ●	Mean number of polyps per patient (MPP) *(primary Outcome)* ADR Advanced ADR >10mm in size Mean adenomas per procedure Polyp detection rate Cancer detection rate Caecal intubation time Withdrawal times Comfort scores	Three patients were excluded due to hyperplastic polyposis discovered during colonoscopy.	Overall, good methodological quality. The primary outcome is mean number of polyps per patient (MPP). There is currently no strong evidence to support an association between MPP and a reduction in CRC. Since the study was only adequately powered to detect differences in MMP the evidence reported on ADR by this study cannot be considered reliable. The study reported approximately double than the average ceacal intubation and withdrawal times for both cohorts. This is a single-centre study. ADR rates reported from

					single-centre studies will be biased by the level of local expertise. Therefore, this study is at high risk for this source of bias and therefore not representative of UK practice as a whole.
Tsiamoulos 2018	Prospective, single centre, non-RCT, follow up period not specified, UK  Endocuff Vision-assisted (EVC) or standard colonoscopy (control) 	410 adults referred with positive FOBt to undergo a BCSP screening colonoscopy. EV= 136 Standard colonoscopy = 274: - pre-cuff = 137 - post-cuff = 137 	ADR Mean number of adenomas detected per procedure (MAP) CIR CIT Negative colonoscopy withdrawal time (NCWT) Conscious sedation level Comfort 	NR	A primary outcome was not specified. No sample size calculation was reported. This is a single-centre study. ADR rates reported from single-centre studies will be biased by the level of local expertise. Therefore, this study is at high risk for this source of bias and therefore not representative of UK practice as a whole.

Rameshshanker 2016	Prospective service evaluation in a single centre, UK Endocuff Vision-assisted (EVC) or standard colonoscopy (control)	96 adult patients undergoing screening colonoscopies EV = 49 Standard colonoscopy = 47	Assess SP6 (adenomas + sessile serrated polyps/adenomas) *(primary outcome)* ADR CIT withdrawal time Number of sessile serrated polyps/adenomas	NR	Study was reported in a conference abstract. There is insufficient information on patient characteristics and study methodology. This is a single-centre study. ADR rates reported from single-centre studies will be biased by the level of local expertise. Therefore, this study is at high risk for this source of bias and therefore not representative of UK practice as a whole.
For each of the 'design', 'participants' and 'outcomes' entries green, amber or red colour coding indicates whether the study matches the scope fully, partially, or not at all: ●●●					

3.4 Overview of methodologies of all included studies

- Two of the included studies were RCTs (Ngu 2018 – ADENOMA, Bhattacharyya 2017 – E-Cap) and 2 were non-RCTs studies (Rameshshanker 2016, Tsiamoulos 2018). All studies were comparative evaluating the intervention specified in the scope against standard colonoscopy.

- Three of the included studies were full text publications and 1 was a conference abstract (Rameshshanker 2016).

- Three of the submitted studies 1 RCT (E-Cap) and 2 non-RCTs (Rameshshanker 2016, Tsiamoulos 2018) involved people attending for screening colonoscopies. In addition the E-Cap RCT also included people for surveillance after removal of polyps. One RCT (ADENOMA) involved a more heterogeneous population, specifically people referred for colonoscopy for clinical symptoms, as part of a post-polypectomy surveillance programme or with positive FOBt as part of BCSP (Ngu 2018). All studies were conducted in UK sites.

- Baseline patient and procedure characteristics were provided in all of the included studies, however, the quality of reporting differed significantly. Highest reporting quality was noted for the ADENOMA RCT and lowest for the Rameshshanker 2016 study that was reported as an abstract. The mean age varied from 61.7 years (ADENOMA) to 68 years (E-Cap). With the exception of the ADENOMA RCT that had a low age limit (>18 years old), the rest of the studies included patients >55 years (Rameshshanker 2016) and >60 years (E-Cap, Tsiamoulos 2018). All included studies had a slightly higher proportion of males and this varied from 53.3% (post-cuff arm, Tsiamoulos 2018) to 68% (SC arm, E-Cap).

- Only the two RCTs provided some information on the bowel preparation and it was similar for the intervention and the comparator. With the exception of the E-Cap RCT that reported unusually high caecal intubation and withdrawal times (approximately 16min and 17-19min, respectively), the ADENOMA and Tsiamoulos 2018 studies reported times comparable to the national BCSP colonoscopy audit (9.4min as reported in Lee 2012). Contrary to the other two studies, E-Cap appears to have been included in the calculation of withdrawal time of both positive and negative colonoscopies, which may explain the longer withdrawal time.

- Only the ADENOMA RCT reported follow-up time (21 days), however, due to the nature on the intervention and the clinical outcomes

associated mostly with the procedure outcome the significance of adequate follow-up is limited in this case. However, this follow-up time is not adequate to detect interval cancer rates. With the exception of ADENOMA all other included studies were single-centre. They were all conducted in secondary care UK settings.

- The 2 RCTs were powered to detect their primary outcome (ADR for ADENOMA, MPP for E-Cap) and they were both single-blinded. Tsiamoulos 2018 used Bonferroni correction to adjust for multiple comparisons. The ADENOMA RCT used an independent Data Monitoring Committee to adjudicate all adverse events. With the exception of the use of hyoscine-n-butylbromide to relax the colon that was more common with EVC, no other statistically significant imbalances in the baseline characteristic between the 2 groups were reported for the RCTs. The non-RCTs studies did not report this information and did not use any adjustment analysis such as propensity score matching.

- All studies evaluated the intervention specified in the scope and used standard colonoscopy as the comparator. All studies reported ADR but only ADENOMA was adequately powered to detect a difference. MAP and PDR were the other most frequently reported outcomes. The primary outcome for E-Cap was the MPP, however, there is no evidence to support a relationship between this outcome and a reduction to CRC rates.

- Three of the included studies (Ngu 2018 - ADENOMA, Bhattacharyya 2017 - E-Cap, Tsiamoulos 2018) provided information on patient-related adverse events.

- Two studies provided subgroup analyses for the BCSP vs. non-BCSP cohorts (ADENOMA) and the BCSP vs. surveillance cohorts (E-Cap). All subgroup analyses reported were pre-planned.

3.5 Overview and critique of the company's critical appraisal

The sponsor's submission used the checklist proposed by NICE for methodological quality assessment of studies. For RCTs, they followed the "CRD's guidance for undertaking reviews in health care" from the Centre for Reviews and Dissemination, University of York, 2008 (Chapter 1, section 1.3.4.). For the non-RCTs studies they used the CASP guidelines.

The EAC carried out a separate quality appraisal of the 4 studies included in the assessment report. The checklist proposed by NICE's guidelines manual (Appendix C) was adapted to fit the intervention methodology. For the non-comparative studies the CASP guidelines were used. A copy of the EACs methodological quality appraisal checklist is included in appendix B.

The EAC's checklist assess the risk of bias in 4 domains categorised as selection bias, performance bias, attrition bias and detection bias. All domains are categorised as low, high, or unclear (risk of bias or applicability). Finally, 1 extra general category was added to assess issues related to conflict of interest, sample size calculations and whether the study was multi-centre and used ADR as the primary endpoint. The results of the assessment are illustrated in Table 7 and Table 8 below.

The EAC's critical appraisal was generally in agreement with the sponsor's. However, some noted differences are reported below:

- The sponsor's critical appraisal does not include an assessment of performance bias due to differences in the procedure. Neither of the RCTs seem to have taken this aspect into account as part of the general question on the similarity of the 2 groups' baseline characteristics. It is noted that in the ADENOMA RCT, the use of hyoscine-n-butylbromide to relax the colon was more common in the EVC group. The use of smooth muscle relaxants, such as hyoscine-n-butylbromide, has previously been shown to have mixed results on the ADR (Rondonotti 2014). As a result there is an unclear risk of performance bias for this study.

- The E-Cap RCT used MPP as the primary outcome. There is currently no strong evidence to support an association between MPP and a reduction in CRC. Since the study was only adequately powered to detect differences in MPP the evidence reported on ADR by this study cannot be considered reliable.

- As shown by the evidence included in section 3.3, also supported by the views expressed by the clinical experts, the effect observed on ADR with EVC is dependent on the colonoscopist's expertise. With higher expertise, EVC is not associated with gains in ADR. As a result, ADR rates reported from single centre studies will be biased by the level of local expertise. The EAC therefore, considered the 3 single centre studies (E-Cap, Rameshshanker 2016, Tsiamoulos 2018) to be at high risk for this source of bias and therefore not representative of UK practice as a whole.

- Finally, the sponsor categorises ADR and MAP as subjective outcomes. However, given their definition (ADR is the percentage of people who are found to have at least 1 adenoma or adenocarcinoma during a screening colonoscopy, MAP is the mean number of adenomas detected per patient) and the need for pathological confirmation the EAC consider these to be objective outcomes.

Table 7: Methodological quality assessment of RCTs

Study	ADENOMA	E-Cap
Selection Bias	Low risk of bias	Low risk of bias
Performance Bias	Unclear/ unknown risk	Unclear/ unknown risk
Attrition Bias	Low risk of bias	Low risk of bias
Detection Bias	Low risk of bias	Low risk of bias
Other (conflicts of interest, power, endpoint, single-centre)	Low risk of bias	Unclear risk of bias

Table 8: Methodological quality assessment of non-randomised studies

Study	Tsiamoulos 2018	Rameshshanker 2016
Is the study based on a representative sample selected from a relevant population?	Yes	Unclear
Are criteria for inclusion explicit?	Yes	No
Did all individuals enter the study at a similar point in their disease progression?	Yes	Unclear
Was follow up long enough for important events to occur?	Yes*	Yes*
Were outcomes assessed using objective criteria or was blinding used?	Yes§	Yes§
If comparisons of sub-series are being made, was there sufficient description of the series and the distribution of prognostic factors?	No	Unclear
*With the exception of adverse events all other outcomes are associated with the procedure therefore the absence of follow-up does not add significant bias to the study. § As stated in section 3.5 ADR is considered an objective outcome.		

3.6 Results

The sponsor included results from 4 studies, 3 published as full text (ADENOMA, E-Cap, Tsiamoulos 2018) and 1 as a conference abstract (Rameshshanker 2016). The EAC accepted all 4 studies for inclusion in the assessment report. The results from these studies are included in Table 9 and Table 10 below.

The mean ADR rates with standard colonoscopy for all included studies (Table 9) was close to the upper range (60%) reported by the national colonoscopy audit indicating centres with high expertise in the procedure (Lee 2012). As noted in the national audit, there is considerable variation in ADR between colonoscopists, ranging from 21.9% to 59.8%. The audit reports a mean of 46.5% which is similar to the 50.9% mean reported in the ADENOMA trial (for the screening population).

Table 9: Included studies ADR and MAP

Study name	Mean ADR	SD or CI	P value	MAP
ADENOMA BCSP cohort*	EVC: 61.7% SC: 50.9% Difference: 10.8%	95% CI: 5.1 to ∞	p=0.001	EVC: 1.59 ± 2.32 SC: 1.2 ± 1.77 (0.39, 97.5% CI: 0.15 to ∞, p=0.004)
ADENOMA non-BCSP cohort	EVC: 24.3% SC: 23.9% Difference: 0.4%	95% CI: -4.1 to ∞	p=0.44	EVC: 0.44 ± 1.24 SC: 0.37 ± 0.8 (0.07, 97.5% CI: -0.04 to ∞, p=0.42)
E-Cap	EVC: 60.9% SC: 63%	NR	p=0.85	EVC: 1.3 ± 1.8 SC: 1.4 ± 1.5 (p=0.54)
Tsiamoulos 2018	EVC: 68% SC: 52.6%	NR	p<0.03	EVC: 2.2 SC: 1.2 (p=0.007)
Rameshshanker 2016	EVC: 83.67% SC: 55.32%	NR	p=0.004	EVC: 1.93 SC: 1.08 (p=NR)
Colonoscopy quality BCSP audit	SC: 46.5%	range: 21.9% - 59.8%		EVC: NR SC: 0.91
*ADR and MAP reported for the whole cohort but authors report no significant differences were noted between the BCSP and non-BCSP cohorts.				

Table 10: Included studies secondary outcomes

Study	Population	Polyp detection rate	Sessile serrated adenomas	Left colon adenomas	Right colon adenomas	Large adenomas (10+ mm)	Small adenomas (6-9mm)	Diminutive adenomas (≤5mm)	Cancer detection rate (all cancers)
Adenoma	Global	EV: 54.1% standard: 48%, P=0.005	EV: 20 (2.3%) standard: 10 (1.1%) p=0.03	EV: 232 (26.1%) standard: 196 (22.2%) p=0.03	EV: 244 (27.5%) standard: 219 (24.8%) P=0.10	EV: 70 (7.9%) standard: 61 (6.9%) p=0.21	EV: 94 (10.6%) standard: 68 (7.7%) p=0.02	EV: 307 (34.6%) standard: 272 (30.8%) p=0.04	EV: 36 (4.1%) standard: 20 (2.3%) P=0.02
	BCSP only	EV: 291 (73.9%) standard: 255 (63.3%) p<0.001	EV: 8 (2.0%) standard: 5 (1.2%) p=0.19	EV: 161 (40.9%) standard: 132 (32.8%) p=0.009	EV: 170 (43.2%) standard: 153 (38.0%) p=0.07	EV: 54 (13.7%) standard: 50 (12.4%) p=0.29	EV: 75 (19.0%) standard: 43 (10.7%) p<0.001	EV: 205 (52.0%) standard: 180 (44.7%) p=0.02	EV: 26 (6.6%) standard: 15 (3.7%) p=0.03
	Non-BCSP only	EV: 189 (38.3%) standard: 169 (35.1%) p=0.16	EV: 12 (2.4%) standard: 5 (1.0%) p=0.05	EV: 71 (14.4%) standard: 64 (13.3%) p=0.31	EV: 74 (15.0%) standard: 66 (13.7%) p=0.29	EV:16 (3.2%) standard: 11 (2.3%) p=0.18	EV: 19 (3.9%) standard: 25 (5.2%) P=0.85	EV: 102 (20.7%) standard: 92 (19.1%) p=0.28	EV: 10 (2.0%) standard: 5 (1.0%) p=0.11
E-cap	Global	EV: 187 (70.3%) standard: 185 (69.8%) p= 0.93	NR	NR	NR	EV: 45 (16.9%) standard: 49 (18.5%) p= 0.81	NR	NR	NR
Rameshshanker	BCSP only	EV: 113 (2.31*) standard:	NR	NR	NR	NR	NR	NR	NR

		62 (1.32*) p<0.001							
Tsiamoulos 2018 had no additional secondary outcomes *Reported as mean number of adenomas per procedure.									

3.7 Description of the adverse events

The sponsor did not run a separate search for adverse events stating that the clinical evidence searches were designed to retrieve all studies irrespective of study design. The EAC agrees with this approach. Three of the studies included in the clinical evidence (Ngu 2018 (ADENOMA), Bhattacharyya 2017 (E-Cap), Tsiamoulos 2018)) provided limited information on patient-related adverse events as shown in table B29 of the manufacturer submission and reproduced below in Table 11.

Ngu (2018) reported 23 adverse events of which 11 were in the EVC cohort, without however providing any detail on the nature of these events. The numbers of adverse events were similar between the 2 groups. The results of the E-Cap study also confirm the above finding with no significant complications observed in either study arm.

The EAC ran additional searches in the MHRA and FDA MAUDE databases (searching “Endocuff”) and found 8 records of adverse events referring to the device as Endocuff rather than referring to a specific version. All incidents were reported between 2/2014 and 09/2015, with one of the incidents taking place in 2014 and possibly reflecting a version prior to EV official CE mark in September 2014. In 7 of the reports Endocuff detached from the colonoscope. Only delays to the procedure were reported due to these incidents and no harm to the patients involved. One report reported the case of a colon perforation during a colonoscopy procedure with Endocuff. The perforation was noted near the end-sigmoid extraction and those present did not attribute this to the Endocuff.

Table 11: Adverse events

Study name (acronym)	Type of colonoscopy	Type of AE or complication	Number analysed	Number of events (%)	Additional details
E-Cap	EVC	NR	265	0	No significant complications observed in either study arm. Postpolypectomy bleeding occurred in one patient in the standard arm. The bleed was identified immediately and was controlled with the application of clips.
	SC		263	1	
ADENOMA	EVC	NR	888	11 (1.2%)	AEs were reported to the Data Monitoring Committee and analysed by two independent clinicians. No AEs were judged to be related to use of EV. Device removal rate was 4.1%, with the most common reason being angulation in a fixed sigmoid colon (52.8%).
	SC		884	12 (1.3%)	
Tsiamoulos 2018	EVC	Anal discomfort	136	2 (1.5%)	No adverse events were reported from the use of Endocuff Vision. It was electively removed in 6 patients where severe sigmoid colon diverticulosis was detected and 2 patients because of discomfort during anal insertion.
	SC (pre-cuff)	NR	NR	NR	
	SC (post-cuff)				
	SC				

3.8 Description and critique of evidence synthesis and meta-analysis

The sponsor did not perform a quantitative synthesis of the included evidence. The reason for not performing a meta-analysis according to the submission was that the E-Cap RCT reported an unusually high ADR, with a baseline rate of 58.9% in the screening population before the start of the trial and demonstrating any increase on this effect would be difficult. The EAC agrees with the sponsor's conclusion, however, for different reasons. The influence of individual expertise on ADR and the loss of a significant effect when EV is used by experienced colonoscopists is demonstrated in the studies included in the submission. The E-Cap RCT found that when individual colonoscopists were analysed, no significant difference was found in ADR between the SC and EV groups. The authors concluded that if endoscopists have a very high ADR in a screening population, then the intervention is unlikely to be of benefit. Tsiamoulos 2018 reported no difference in the ADR when the results from each colonoscopist were analysed separately. The EAC also requested input from clinical experts with regards to this matter, they supported the published evidence cited above and noted that is it likely that the increase in ADR seen with EV could be different between experienced and less experienced endoscopists, with the former group not showing much benefit because their baseline ADR is already high.

A recently published meta-analysis supports the above findings and input from clinical experts showing that the effect of high ADR on the efficacy of Endocuff-assisted colonoscopy was noted in the previous version of the device as well (Williet 2018). The meta-analysis, that includes studies using both EV and the previous version, showed that the ADR was significantly increased in the Endocuff-assisted colonoscopy vs. SC group only for operators with low-to-moderate ADRs (<35%). In contrast, this benefit was not reached for operators with high ADRs (>45%).

3.9 Ongoing studies

The sponsor included 9 ongoing studies (Table 12), none of which have any results available. The EAC ran additional searches (see Appendix A for details) and identified a further 5 ongoing studies, none of which have any results available.

Table 12: Ongoing studies

Trial ID	Full record	Intervention	Clinical Trials Status
NCT03418948 2017	Radboud University. (2017). Comparison of AMR and ADR between Endocuff vision-assisted and conventional colonoscopy: a multicenter randomized trial (EXCEED). Bethesda: US National Library of Medicine. Available from https://clinicaltrials.gov/ct2/show/NCT03418948 Identifier: NCT03418948	Endocuff Vision	Recruiting
NCT03398447 2018	New York University School of Medicine. (2018). High-definition white-light colonoscopy versus high-definition white-light colonoscopy with Endocuff vision for Endpoints of procedural times, 40 Years. Bethesda: US National Library of Medicine. Available from https://clinicaltrials.gov/ct2/show/NCT03398447 Identifier: NCT03398447	Endocuff Vision	Recruiting
NCT03361917 2017	Indiana University. (2017). Standard colonoscopy versus colonoscopy with Endocuff vision, 40 Years. US National Library of Medicine: Bethesda. Available from https://clinicaltrials.gov/ct2/show/NCT03398447 Identifier: NCT03361917	Endocuff Vision	Recruiting
NCT03344055 2017	Société Française d'Endoscopie Digestive. (2017). Endocuff-assisted colonoscopy vs standard colonoscopy on adenoma detection rate, 18 Years. Bethesda: US National Library of Medicine. Available from: https://clinicaltrials.gov/ct2/show/NCT03361917 Identifier: NCT03344055	Endocuff Vision	Recruiting
NCT03117114 2017	Technische Universität München. (2017). Endocuff vision assisted vs. standard polyp resection in the colorectum, 18 Years. Bethesda: US National Library of Medicine. Available from: https://clinicaltrials.gov/ct2/show/NCT03117114 Identifier: NCT03117114	Endocuff Vision	Not yet recruiting
NCT03072472 2017	South Tyneside NHS Foundation Trust. (2017). BowelScope: accuracy of detection using Endocuff optimisation of mucosal abnormalities, 55 Years. Bethesda: US National Library of Medicine. Available from: https://clinicaltrials.gov/ct2/show/NCT03117114. Identifier: NCT03072472	Endocuff Vision	Recruiting
ACTRN12617001364369 2017	Box Hill Hospital Victoria. (2017). Endocuff-vision assisted chromoendoscopy for surveillance for cancer and dysplasia in inflammatory bowel disease, 18 Years. Sydney: National Health and Medical Research Council (NHMRC) Clinical Trials Centre - University of Sydney. Available from: https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=373642. Identifier: ACTRN12617001364369	Endocuff Vision	Recruiting

Trial ID	Full record	Intervention	Clinical Trials Status
Fang 2017	Fang W, Haridy J, Keung C, et al. (2017) Endocuff vision-assisted colonoscopy for surveillance of cancer and dysplasia in ulcerative colitis. Journal of Gastroenterology and Hepatology (Australia) 32(Suppl 2),pp. 22.	Endocuff Vision	Unknown
Jacob 2017	Jacob A and Hewett P (2017) Comparing standard colonoscopy to Endocuff vision assisted colonoscopy: a randomized control trial with video analysis. Diseases of the Colon & Rectum 60(6),pp. E463-E464.	Endocuff Vision	Expected to complete in Jan 2017 but not further information available
New ongoing studies identified by the EAC			
NCT03442738 2018	Universitätsklinikum Hamburg-Eppendorf (2018) A Prospective Randomized Comparison of the Adenoma Detection Rate With a Disposable Cap (ENDOCUFF VISION®) (Endocuff) https://clinicaltrials.gov/ct2/show/study/NCT03442738	Endocuff Vision	Recruiting
UMIN000032118	Wada Clinic (2018) Randomized comparison of surveillance after colonoscopic removal of adenomatous polyps: Endocuff-assisted colonoscopy versus the standard colonoscopy https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000036641	Endocuff (it is not clear which version of Endocuff is used)	Recruiting
NCT03560128 2018	Indiana University (2018) Endocuff Vision Colonoscopy vs. AmplifEYE Colonoscopy https://clinicaltrials.gov/ct2/show/NCT03560128	Endocuff Vision	Recruiting
NCT03560037 2018	University of California, Davis (2018) Use of a Distal Colonoscope Attachment to Increase Detection of Sessile Serrated Adenomas https://clinicaltrials.gov/ct2/show/NCT03560037	Endocuff Vision	Recruiting
NCT03436004 2018	Dr. Alberto Herreros de Tejada Echanojáuregui (2018) Evaluation of Colonoscopy With a Specific Device for the Detection of Adenomas (ENDOCOLES) https://clinicaltrials.gov/ct2/show/NCT03436004	Endocuff Vision	Recruiting

4 Economic evidence

4.1 Published economic evidence

Critique of the company's search strategy

The sponsor conducted an economic evidence search on Embase, Ovid MEDLINE (including in process), Cochrane Database of Systematic Reviews (CDSR), Cochrane Central register of Controlled Trials (CENTRAL), Database of Abstracts of Reviews and Effects (DARE), Health Technology and Assessment (HTA) Database, NHS Economic Evaluation Database (NHS EED) and EconLit for articles published over the period 2010 to present. Articles prior to 2010 were excluded on the grounds that they predate the availability of EV. The above database searches were supplemented by further searches of relevant conference proceedings not included within Embase and the grey literature. The following clinical trial registries were searched: Clinicaltrials.gov; World Health Organisation International Clinical Trials Registry Platform; UK Clinical Trials Gateway. References of relevant publications were also checked.

After de-duplication 3497 records were identified of which 122 were assessed for inclusion after title/abstract screening. Only one record was deemed relevant. The majority of exclusions were ascribed to an ineligible intervention/ comparator (73) or ineligible study design (33).

The EAC reviewed the search strategy (Appendix 1 of manufacturer's submission) and found it to be appropriate. The EAC updated the search to cover the period between the sponsor's search and July 2018. However, no additional relevant records were retrieved (see section 3.1).

Critique of the company's study selection

The sponsor included studies on adults receiving colonoscopy for surveillance or diagnostic reasons in which Endocuff or Endocuff Vision was evaluated in a non-comparative study or in comparison with standard endoscopy. Studies were included provided they reported relevant outcomes. Relevant outcomes included detection rates, duration of colonoscopy, complications and adverse events and long term outcomes (including tumour recurrence and referral rates.) Non-English and pre 2010 studies were excluded. The EAC reviewed the inclusion and exclusion criteria and concluded that they were appropriate.

Included and excluded studies

The sponsor's search yielded a single relevant economic study which was published as a conference poster.

Overview of methodologies of all included economic studies

The included study is a cost-consequences analysis which modelled the cost of colonoscopy and the downstream treatment costs of CRC with and without the use of EV. All patients were assumed to undergo bowel preparation with polyethylene glycol and ascorbate citing a recent trial indicating superiority to sodium picosulphate/magnesium citrate (Pohl 2015). Use of EV was assumed to increase ADR by 11.7% based on results from two RCTs comparing Endocuff colonoscopy with standard colonoscopy (Biecker 2015; Floer 2015). Individuals were simulated over a period of ten years to estimate progression of CRC in the presence of screening with and without EVC. Costs were discounted at 3% per annum. The use of Endocuff Vision generated additional costs of €2,651,953 (2015 Euros) for a cohort of 10,000 patients. The authors report the avoidance of 183 CRC cases generating savings of €5,138,755 at a treatment cost of €28,080 per case. Further modest savings are reported 'related to CRC treatment occurrence'; the source of these savings is unclear. The net cost result is a total cost saving €2.9m for the cohort.

Overview and critique of the company's critical appraisal for each study

The sponsor applied no formal quality appraisal to the single selected study on account of publication in abstract form only. The EAC was able to access a poster describing the study, in addition to the abstract. However, the EAC also considered the available reporting insufficient to justify a quality appraisal.

Does the company's review of economic evidence draw conclusions from the data available?

The company noted that the single study included in the review found cost savings attributable to Endocuff but viewed the findings to be of limited relevance due to the German setting and the use of data from a trial of Endocuff rather than Endocuff Vision. The EAC accepts this judgement.

4.2 Company de novo cost analysis

The sponsor submitted estimates of the cost impact of EVC in the UK based on a de novo cost model. The model consists of a number of interlinked decision trees and Markov models and is based on a model of colorectal cancer (CRC) that has been used in previous economic evaluations of CRC screening programmes (Tappenden 2007; Whyte 2012; Murphy 2017REF).

Cured patients do not re-enter the model; follow-up screening costs for CRC survivors are assumed to be included in the treatment costs.

The model captures the cost of colonoscopy, FOBT and CRC treatment according to stage at diagnosis. The impact of failed colonoscopy is captured by adjustment of the costs of colonoscopy to include a proportion of repeat procedures. Costs are discounted at 3.5% and summed over ten years.

Patients

The analysis estimates costs over ten years for a cohort of 62 year olds undergoing surveillance colonoscopy as a result of a positive FOBT test. This represents patients undergoing colonoscopy as a result of their participation in the bowel cancer screening programme (BCSP). This is a subgroup of the population specified in the scope.

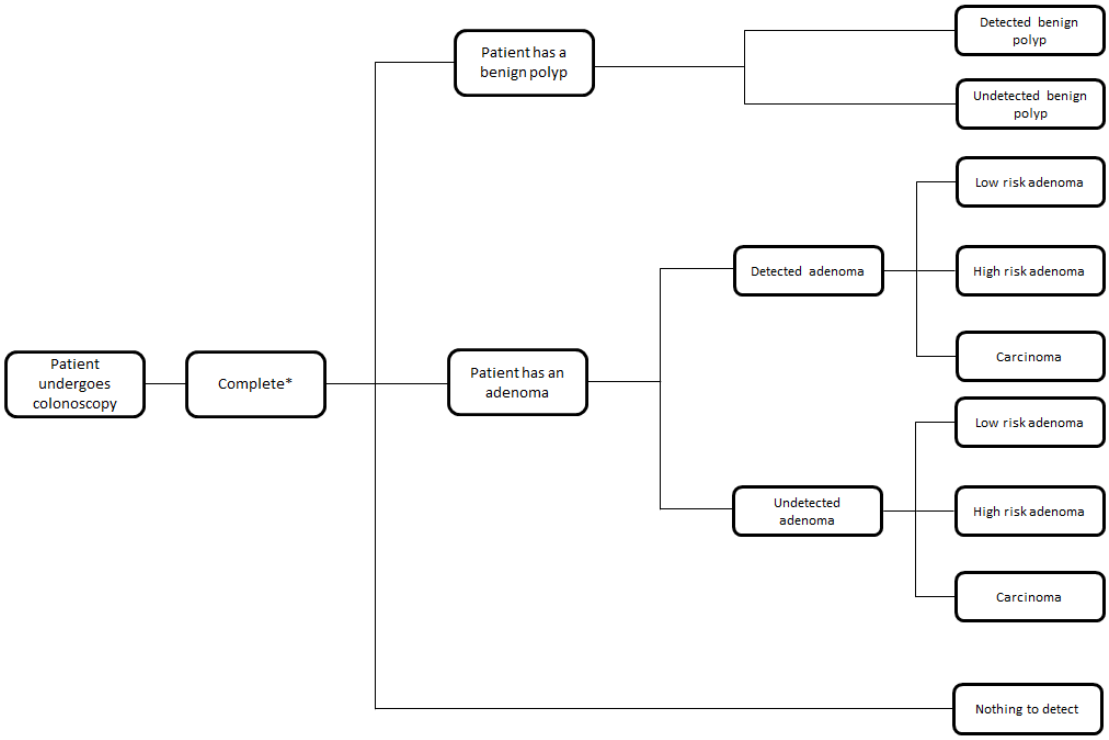
Technology & Comparator(s)

The technology evaluated is EVC. It is compared with standard colonoscopy, which is colonoscopy without the use of an additional device on the end of the probe to aid visualization of the colon.

Model structure

The sponsor's cost analysis utilizes a Markov model of CRC. The model follows the natural history of the disease from the formation of a polyp through to low and then high risk adenomatous polyps and then to CRC. The stages of CRC are not modelled explicitly. Rather a single health state (occupied for a maximum of one year) is used to capture CRC with survivors progressing to a post CRC 'cured' state. Cured patients do not re-enter the model; follow-up screening costs for CRC survivors are assumed to be included in the treatment costs. It is implemented as a series a sub-models to which patients are assigned according to their risk group and associated colonoscopy recall period following their initial colonoscopy. The use of multiple models allows the implementation of different follow-up colonoscopies for patients according to their risk status determined by the initial colonoscopy. The model incorporates the impact of FOBT testing with colonoscopy follow-up of positive results in the BCSP in addition to the impact of colonoscopy surveillance for patients following removal of a cancerous polyp. Patients without adenomas are invited for FOBT screening every two years. Patients judged to be at low risk are recalled for colonoscopy screening after five years; patients judged high risk are recalled every year. A decision tree is used to determine the impact of colonoscopy (either standard or with Endocuff Vision) on polyp identification, and the subsequent risk status and colonoscopy recall interval for the patient. Patients are assumed to undergo removal of polyps and adenomas at the time of colonoscopy. Patients undergoing initial screening with EVC are assumed to undergo all subsequent colonoscopies with Endocuff Vision, and likewise for patients receiving an initial screen using standard colonoscopy. The structure of the decision tree and the Markov model is shown in * A small proportion of people have an incomplete colonoscopy. These people are assumed to undergo a second colonoscopy within the same cycle (year). The additional cost of the failed colonoscopy is captured within the model.

Figure 2 and Figure 3 below,



* A small proportion of people have an incomplete colonoscopy. These people are assumed to undergo a second colonoscopy within the same cycle (year). The additional cost of the failed colonoscopy is captured within the model.

Figure 2: Decision tree to determine patient pathways following screening colonoscopy.

Figure 3: Markov model of the natural progression of CRC.

* A small proportion of people have an incomplete colonoscopy. These people are assumed to undergo a second colonoscopy within the same cycle (year). The additional cost of the failed colonoscopy is captured within the model.

- Figure 2: Decision tree to determine patient pathways following screening colonoscopy.
- Figure 3: Markov model of the natural progression of CRC.
- Patients enter the model at age 62 and are followed for ten years. Costs are estimated for screening and for treatment of CRC. Only costs falling on the health care sector are included. Costs arising after the first year are discounted at the recommended rate of 3.5% per annum.

The model makes some simplifying assumptions:

- Intermediate risk following colonoscopy and polyp removal is not explicitly modelled; intermediate and high risk patients are combined and modelled as high risk
- CRC mortality and CRC treatment costs are captured using a single health state over one year

- All-cause mortality is not separately estimated in the year in which patients have CRC. Rather a single mortality estimate is used to capture mortality in that year and excess mortality from CRC in subsequent years

- The specificity of colonoscopy is assumed to be 100%

- Patients with incomplete colonoscopy undergo a further colonoscopy which is assumed to be complete. Colonoscopy costs are adjusted to account for repeated use after incomplete procedures

- Patients are assumed to present with symptoms in the year they develop an undetected CRC. However, the stage distribution assumed for these undetected cancers reflects that of patients presenting with symptoms rather than that for screen detected CRC

- Patients who drop out of high risk surveillance do not return

- CRC stage at detection by colonoscopy will not be affected by the use of Endocuff Vision

- The proportion of undetected adenomas that are low risk, high risk or CRC is assumed to be the same as that for detected adenomas in patients receiving endoscopy with Endocuff Vision during the learning curve for endoscopists. Proficient endoscopists are assumed to detect all adenomas present with Endocuff Vision

- The model assumes that the use of Endocuff Vision does not change the time taken to perform a colonoscopy, although it is likely to increase the number of polypectomies performed during scoping

The EAC notes the complexity of the model but believes that the approach is necessary to capture the impact of EVC on CRC treatment costs arising from upstaging. Such costs are likely to be an important consideration. Overall, the EAC thinks that the model structure, time cycle and time horizon are appropriate for this assessment.

Summary of the base case

The sponsor's base case results are reported in Table 13. The sponsor estimates a cost saving of £12 per patient over a period of ten years. The sponsor did not undertake any subgroup analysis.

Table 13: Sponsor's base case results

	Expected cost (£)	Cost difference (£) per patient
Endocuff Vision colonoscopy	1,532	-
Standard colonoscopy	1,544	12

Clinical parameters and variables

Clinical parameters are sourced from the available literature. The recent ADENOMA trial was favoured for those parameters which could be determined from the study (Ngu 2018). The model is based on an established CRC model for which the parameters governing transitions were estimated through calibration. The EAC notes that this is standard practice in cancer modelling where observation of the progression of the disease is not feasible. Expert clinical advisers were consulted on the structure of the model and appropriate sources for some key parameters.

- Estimates of compliance with surveillance colonoscopy, FOBT screening and colonoscopy following a positive FOBT screen are taken from a previous evaluation of FOBT testing (Whyte 2012)

- Estimates of the probability of a positive FOBT result according to adenoma status are based on sensitivity and specificity estimates for FOBT reported in Whyte (2012). This data has been inappropriately applied in the model.

- The proportion of failed endoscopies and the detection rate for adenomas and benign polyps for both EVC and standard colonoscopy is taken from data reported from the ADENOMA trial (Ngu et al. 2018). The EAC notes that the rate of failed endoscopies reported from an audit of the BCSP is higher than that recorded in the ADENOMA trial which would indicate that this parameter has been underestimated

- Transition parameters for the development of low risk adenomas and transition from low risk to high risk adenomas are derived from a calibration exercise undertaken during development of the model for a previous application (Whyte 2012)

- Transition from high risk adenoma to CRC as a function of age category is taken from an appropriate literature source (Brenner 2007)

- The probabilities of adenoma recurrence as a function of the risk category of the patient (low/high) and the time after initial adenoma (dichotomised as year 1 or years 2+) are referenced to a previous incarnation of the model (Tappenden 2007). The ultimate source of this data was a randomised trial comparing follow-up of patients at either 1 and 3 years or 3 years only following detection of an adenomatous polyp (Winawer 1993)

- All-cause mortality as a function of age has been derived from appropriate national sources (Office for National statistics 2016)

- CRC mortality has been estimated from data in McPhail (2015). The methods used to estimate this are unclear but may have been based on calculations utilising all-cause mortality data by age and sex and the excess mortality relative risk reported in McPhail.

- A learning curve for EVC is assumed on the basis of an estimation of the number of colonoscopists who would perform 1,000 colonoscopies taken from data in Shenbagaraj et al. (2018) and an assumption that 20 colonoscopies are required to achieve proficiency in line with exclusion criteria for the ADENOMA trial (Ngu 2018)

The EAC considers the model to be appropriate for the assessment of the impact of this technology on CRC development in patients. The ADENOMA trial is an appropriate source to estimate detection rates with standard colonoscopy and colonoscopy with Endocuff Vision and the difference in proportions of successful colonoscopies with and without Endocuff Vision. The EAC notes that the proportion of successful colonoscopies in routine practice appears to be lower than that reported in the ADENOMA trial, and that a reduction in this proportion would reduce the cost saving attributable to Endocuff Vision. Where possible model parameters for the development of CRC have been drawn from the literature. The EAC has checked these sources and considers them to be appropriate. Parameters have been estimated through calibration with observed CRC outcome data where necessary. It is not possible for the EAC to assess the robustness of this exercise. However, the model developers have a recognised pedigree in the development of models of cancer and the use of calibration to estimate parameters governing the natural history of the disease. The parameterisation of the sensitivity and specificity data taken from Whyte (2012) for the FOBT test is incorrect, resulting in an underestimation of the false positive rate and the true positive rate for patients with high risk adenomas.

Resource identification, measurement and valuation

There are two main cost parameters in the model: screening costs and CRC treatment costs. Costs are applied in 2016/17 GBP. Colonoscopy costs are derived from NHS reference costs according to whether polyps are identified or not (NHS Improvement 2017). Costs of FOBT tests according to whether the patient tests positive, negative or does not return a stool sample are derived from a previous evaluation of FOBT testing (Whyte et al 2012) and inflated to 2016/17 values. The EAC considers these sources of cost data to be appropriate.

The sponsor has tabulated the results of their search on the source of cost data on the treatment of CRC cancer. A number of publications apply this data but many cite the same sources so that the number of original estimates is modest. All show increasing costs with diagnosis of CRC at a later stage, but the magnitude of the differences varies across sources. The sponsor has chosen to derive treatment costs by stage from a recent cost study undertaken by Incisive Health (Incisive Health 2014). This study has the advantage that the cost estimates reported include costs for the treatment of recurrent disease. The cost estimates reported by Incisive Health are similar to estimates reported in most of the other primary sources of cost data, including those used in the development of NICE guideline NG12, but are higher than the estimates reported by Whyte et al. (2012b). The sponsor has undertaken sensitivity analysis in which alternative cost sources are considered. The EAC has examined the different costs sources and considers the use of cost data from Incisive Health to be appropriate.

In order to estimate the cost of treating screen detected CRC and CRC detected symptomatically, CRC treatment costs by stage are combined with data on the stage distribution for screen detected and symptomatic CRC in Wiegering (2016). These data are taken from Germany. Comparable data from the UK were only available in abstract form (Sagar 2015). The sponsor also considers data reported from a larger study in the Netherlands (Toes-Zoutendijk 2017). In the German data, the screened population received screening with endoscopy. The UK abstract reports data from the BCSP where patients are screened with endoscopy following a positive FOBT test. The Dutch data reports stage in patients screened following a positive FIT test. The EAC considers the UK and Dutch data to be more relevant to analysis of patients in the BCSP, dependent on the faecal test preceding endoscopy. Both the Dutch and English data indicate detection at an earlier stage with screening compared to the German data and hence a larger cost saving in terms of treatment costs. The difference between the English and Dutch data, in terms of the impact of screening on treatment costs of CRC, is modest. The EAC considered the German data to be more relevant to a non-BCSP population where adenoma rates are likely to be lower, but notes that none of the three data sources are ideal for this population.

Technology and comparators' costs

The UK list price for Endocuff Vision is £12.05. The sponsor's analysis assumes that the additional cost of a colonoscopy using Endocuff Vision is simply the cost of the sleeve (£12.05). This implicitly assumes that EVC does not change the time taken to undertake a colonoscopy. This assumption is supported by data reported in the ADENOMA trial (Ngu et al. 2018). The additional cost of colonoscopy with Endocuff Vision is also dependent on the number of unsuccessful colonoscopies, and hence repeat procedures. The sponsor's model has used data from the ADENOMA trial (Ngu et al. 2018) to estimate this. The EAC notes that estimates from the BCSP are higher than those reported in the ADENOMA trial.

Sensitivity analysis

The sponsor has undertaken both deterministic and probabilistic sensitivity analysis. Three structural assumptions were examined. Sensitivity analysis was undertaken on the impact of the assumption that treatment costs for CRC accrue over a single year. An alternative assumption in which costs were assumed to be equally distributed over the first two years had a modest impact on the overall costs, generating a cost saving for EVC of £9 per patient. The impact of a learning curve for the increased effectiveness of colonoscopy with Endocuff Vision was explored in sensitivity analysis. Removal of the learning curve increased the cost saving for Endocuff Vision to £19 per patient. Finally, the recall interval for patients judged to be low or high risk was varied over the range 1-3 years for high risk patients and 3-9 years for low risk patients. When the recall interval for low risk patients was reduced to three years (from the base case of 5 years) overall costs of endoscopy with Endocuff Vision were higher than costs with standard endoscopy. The difference in costs at a recall interval of three years, as evidenced in the Tornado plot in the sponsor's submission, was small.

Deterministic sensitivity analysis was undertaken on key model parameters. Thresholds are reported where the range of the parameter includes values at which the direction of cost savings changes. Parameter ranges for sensitivity analysis were determined from 95% confidence intervals in the source literature, where possible, or were varied from +20% to -20% of the mean value. The EAC notes that while the use of a range from ±20% of the mean is commonplace it may not represent the likely range of uncertainty for some parameters.

Parameters varied in the deterministic sensitivity analysis are discussed in detail below.

- The proportion of men in the cohort was varied from 0 to 100%

- The proportion of successful colonoscopies was varied separately for standard colonoscopy and for colonoscopy with Endocuff Vision over the range 78.2% to 100%. The lower value is 20% less than the base case values

- Probabilities of adenoma recurrence according to risk category (low/high) and year of follow-up (first year or subsequent years) were varied over the range ±20%

- Annual transition rates for the progression of CRC were varied over the range ±20%

- The ADRs for colonoscopy with and without using Endocuff Vision were varied over the range ±20%

- Costs of colonoscopy were varied separately for standard colonoscopy and for colonoscopy with Endocuff Vision using the lower and upper quartile values of the range reported for colonoscopy with and without removal of polyps in the NHS Reference Costs (NHS Improvement 2017)

- The impact of the costs of CRC treatment detected through screening and through symptomatic presentation were investigated by varying the cost of treating CRC detected through screening and varying the additional costs of treatment in patients presenting symptomatically. In each case the ranges used were derived from the lowest and highest values across the range of values of treatment costs for CRC reported in the literature

- The number of colonoscopies required to achieve proficiency was varied over the range ±20%

- The proportion of patients complying with FOBT tests and the proportion of patients complying with surveillance colonoscopy following a positive FOBT test or as part of a screening programme according to risk status was varied from 20% less than the base case value to 20% more or an upper bound of 100% for base case values above 80%

- The probabilities of requiring a colonoscopy according to risk status (normal/low/high) were varied over the range ±20%

- The costs of FOBT tests according to whether the test was returned and the result (positive/negative) were varied over the range ±20%

- The stage distribution of CRC in patients detected at screening and those missed at screening was varied across ranges of approximately ±50%

- Scenario analysis was undertaken in which the stage at detection for screen detected and symptomatic CRC was taken from data collected in the UK (Sagar 2015)

In addition to deterministic sensitivity analysis a probabilistic sensitivity analysis (PSA) was run with mean cost differences estimated over 2,000 runs of the model with values for each parameter sampled from distributions. Beta distributions were selected for the proportion of successful colonoscopies and for the polyp detection rate with and without Endocuff Vision. Beta distributions were also selected for the probability of requiring a colonoscopy for patients categorized as normal, low or high risk. Lognormal distributions were selected for transition parameters describing the development of CRC and the mortality rate for CRC. Dirichlet distributions were applied to the proportion of patients categorized as normal/low risk/high risk/CRC following colonoscopy. Gamma distributions were applied to costs, including the cost of treatment of screen-detected CRC and the additional cost of treating CRC in patients presenting symptomatically. The EAC considers the distributions selected to be appropriate, but notes that the Gamma distribution for the ADR gain with ENDOCUFF VISION has been parameterised incorrectly. The one-sided confidence interval reported in the ADENOMA trial (Ngu 2018) appears to have been incorrectly interpreted. The true standard error on the gain in ADR reported by Ngu (2018) is larger than that estimated by the sponsor with the result that the sponsor has underestimated the variability of this parameter in their PSA.

The probabilistic analysis did not vary the proportion of patients with detected adenomas (or the proportion of patients with undetected adenomas) falling into the normal/low risk/high risk/CRC categories in the main PSA. However, a limited further PSA was run in which the proportions were allowed to vary under constraints to ensure that the parameter values selected were mathematically tractable and biologically feasible.

The sponsor presented the results of the deterministic sensitivity analysis in the form of a Tornado Plot. The parameters for the cost of colonoscopy with and without Endocuff Vision and the proportion of successful colonoscopies with and without Endocuff Vision had the largest impact on the overall cost impact of Endocuff Vision. The EAC considered it unlikely that the cost of

colonoscopy would differ for colonoscopy with and without Endocuff Vision apart from the cost of the Endocuff Vision sleeve. The EAC also considered it unlikely that the proportional of successful colonoscopies would vary according to the use of Endocuff Vision beyond the differences reported in the ADENOMA trial of 0.1% (Ngu et al. 2018). Hence the EAC considered that this sensitivity analysis did not indicate a significant risk to the base case finding that Endocuff Vision is cost saving.

The next parameters with the largest impact on overall cost are the ADR rates for colonoscopy with and without Endocuff Vision. The deterministic analysis indicates variation in the overall cost impact of Endocuff Vision from a cost decrease of around £60 to a cost increase of around £40 when either of the parameters are varied over the ranges derived from data in the ADENOMA trial (Ngu et al.2018). The EAC considers this analysis to show that the overall cost impact of EVC is sensitive to the extent of the improvement in ADR. A number of other parameters had a more modest impact on overall cost but were sufficient to change the direction of cost savings (standard colonoscopy became cheaper) for some values across the ranges considered.

The sponsor's threshold analysis indicates that the improvement in ADR with EVC must exceed 8.35% for Endocuff Vision to be cost saving. The sponsor notes that this is within the one-sided 95% CI for the parameter reported in the ADENOMA trial (Ngu et al. 2018). At the lower interval of the difference in the ADR rate between standard colonoscopy and colonoscopy with Endocuff Vision of 5.1% the overall impact of the use of Endocuff Vision is to increase costs by £15.The analysis indicates that a saving in treatment costs of CRC through earlier detection of a minimum of £1,241 is required for Endocuff Vision to be cost saving. The sponsor notes that the estimated cost saving, which is based on the difference in stages for screen detected and symptomatic CRC reported in Wiegering et al. (2016) and treatment cost by stage, is lower than £1,241 when calculated using some of the sources of CRC treatment costs by stage. The sponsor reports threshold values for cost of colonoscopy and the proportion of successful colonoscopies with and without Endocuff Vision but notes that both parameters are unlikely to vary much according to whether or not Endocuff Vision is used. The EAC agrees with this assessment. The scenario analysis in which stage data for screen detected and symptomatic CRC was taken from a UK based study (Sagar 2015) generated a cost saving for Endocuff Vision of £56. In two-way sensitivity analysis in which alternative sources were considered for both the stage distribution of screen detected and symptomatic CRC and the cost of treating CRC by stage, Endocuff Vision was cost saving in each of the scenarios except those which used treatment cost data from Picot (2017) and Whyte (2012b).

The probabilistic analysis generated a mean cost saving of £12 for Endocuff Vision. Endocuff Vision was cost saving in 77% of simulations.

4.3 Interpretation of economic evidence

The sponsor's de novo costs analysis indicates a saving of £12 per patient for a cohort of patients undergoing colonoscopy at age 62. The cost saving is lower than the value reported by Conway (2015) in their model-based analysis in a German setting. However, the results are consistent with the available literature with regard to the direction of the cost saving.

4.4 Results of EAC analysis

The EAC considers the basic structure of the sponsor's model to be robust. The EAC has noted two occasions where it would have selected a different parameter source to that chosen by the sponsor: the failure rate for colonoscopy and the stage distribution for screen detected and symptomatic CRC. The EAC also noted some minor errors in the execution of the sponsor's model. The EAC revised the sponsor's model in the following three ways. Firstly, it amended the errors noted in section 4.2, primarily the application of data on the sensitivity and specificity of the FOBT test. Second, it revised the success rate for standard colonoscopy to 95.2%, matching that reported in an assessment of the BCSP (Lee 2012). The success rate for endoscopy with Endocuff Vision was assumed to be 0.1% lower as reported in the ADENOMA trial (Ngu 20178). Third, it utilised data from the UK including BCSP patients (Sagar 2015) to parameterise the stage distribution of screen detected and symptomatic CRC.

Base-case analysis results

The EAC's modified model estimates a saving of £52.74 per patient in the BCSP. Reduction of the success rate for colonoscopy lowers the cost saving attributable to Endocuff Vision by a modest amount. Correct parameterisation of sensitivity and specificity of the FOBT test had minimal impact on overall costs. By far the largest impact is attributable to the use of stage data on screen detected and symptomatic CRC from the UK (Sagar 2015).

Sensitivity analysis

The sponsor's submission identified the gain in ADR from Endocuff Vision as a key parameter. The EAC undertook sensitivity analysis in which it reduced the ADR gain attributable to Endocuff Vision. The EAC made some structural changes to the model to implement this sensitivity analysis. The EAC retained the assumption that colonoscopy with Endocuff Vision has a sensitivity of 100% (i.e. with experience the endoscopist detects all Adenomas). (This assumption in combination with a reduced ADR gain attributable to Endocuff Vision simulates a cohort with a lower overall number of adenomas.) The EAC altered the model to ensure the same proportion of adenomas classified as

low risk, high risk or CRC in the detected and undetected branches of the standard endoscopy arm and the detected and undetected branches of the Endocuff Vision arm as the gain in ADR for Endocuff Vision was varied. (Note that in the base case analysis submitted by the sponsor the distribution of low risk, high risk and CRC adenomas is the same for the cohort in the treatment and comparator arms.) This modification assumes the likelihood that an adenoma is missed is not dependent on the risk status of the patient. In practice it seems likely that smaller adenomas would be more likely to be missed, and patients with smaller adenomas may be more likely to be classified as low risk (Quality Assurance Guidelines for Colonoscopy). When the gain in ADR attributable to Endocuff Vision was reduced to 5.1%, the limit of the one sided 95% CI reported in the ADENOMA trial (Ngu 2018), it remained cost saving. The overall cost saving per patient was £13.54. Endocuff was cost neutral at an ADR gain of 3.0% (i.e. Endocuff Vision must increase ADR by at least 3% to offset the additional costs of its use through a reduction in CRC treatment costs).

The EAC undertook two-way sensitivity analysis on the cost of CRC treatment by stage and the stage distribution of CRC in screen detected and symptomatic patients. The EAC explored each of the sources of treatment costs identified by the sponsor and examined in their sensitivity analysis. These were combined with German, UK and Dutch stage distribution data for screen detected and symptomatic CRC. Table 14, below, presents the costs associated with Endocuff Vision in each of the sensitivity analyses. The analysis draws the same conclusions as the original sensitivity analysis undertaken by the sponsor. Cost savings are larger when the English or Dutch data (in which a positive faecal test precedes screening colonoscopy) on CRC stage distributions are applied, but the direction of cost savings is only influenced by the source of CRC treatment costs by stage. Endocuff Vision is cost saving for each of the sources of CRC treatment costs by stage except two. (There is one exception to this – the combination of the Department of Health (2011) estimates for treatment costs of CRC by stage generates a positive cost for Endocuff Vision only in combination with the German stage data.) The EAC concludes that this analysis illustrates the sensitivity of estimates of the cost impact of Endocuff Vision to the difference in treatment costs for early and later stage CRC. However, the majority of sources of this data generate results in agreement with those generated using the cost estimates from Incisive Health (2014).

	Stage distribution of CRC at detection		
Treatment cost sources	Sagar 2015	Wiegering 2016	Toes-Zoutendijk 2017

NICE diagnostic guidance (2016) / Picot (2017) 60-69 years	**£10.11**	**£22.37**	**£10.25**
Public Health England (2016)	-£43.09	-£13.53	-£47.23
NICE NG12 (2015)	-£74.31	-£7.58	-£70.93
Incisive Health (2014)	-£52.74*	-£8.79	-£54.16
Whyte (2012)	-£116.92	-£60.53	-£121.90
NICE CG118 (2011)	-£95.78	-£50.94	-£101.00
Department of Health (2011)	-£62.87	**£0.09**	-£58.02
Lee (2012)	-£79.84	-£11.84	-£76.76
Westwood (2017)	-£105.96	-£20.97	-£101.65
Murphy (2017)	-£115.92	-£59.89	-£120.87
EEPRU (60 to 69 years)	**£10.14**	**£22.38**	**£10.27**

*Base case parameters. Parameter combinations generating positive (increased) costs for Endocuff Vision highlighted in bold.

The EAC also undertook scenario analysis in which routine screening is undertaken using FIT rather than FOBT. To do this it made the following amendments to the sponsor's model. The costs of faecal screening for non-compliant patients and after a negative and positive result were amended to £6.88, £7.88 and £17.33, respectively, based on the cost of the FIT reported in Whyte (2012) and inflated to 2016/17 values. The sensitivity of the faecal test for low and high risk adenomas was amended to 5% and 32%, respectively, based on the data in Whyte (2012). The specificity of the faecal test was amended to 93% based on the data in Whyte (2012) for patients aged 70. Finally, the stage distribution of CRC in screen detected and symptomatic CRC was amended to match that reported in the Dutch study of screening with FIT prior to colonoscopy (Toes-Zoutendijk 2017). (Note: this data was similar to the UK data from the BCSP reported in Sagar 2015). In

this scenario analysis the cost saving attributable to Endocuff Vision increased to £57.53.

Subgroup analysis

The sponsor's analysis considered only patients in the BCSP. The ADENOMA trial (Ngu 2018) reported data for patients screened as part of the BCSP and patients whose screening was not part of the BCSP. For the latter group the improvement in ADR observed in the Endocuff Vision arm was 0.4%. The EAC undertook a subgroup analysis in which it considered the cost impact of Endocuff Vision in this population based on the results of the ADENOMA trial. It modified the ADR gain associated with Endocuff Vision to 0.4%. It also parameterised the stage distribution of screen detected and symptomatic CRC using the German data (Wiegering 2016) in which patients screened using endoscopy (without a prior positive faecal test) were compared with patients presenting with symptoms. Finally, the EAC changed the proportion of successful standard colonoscopies to 92.3% to reflect the unadjusted caecal intubation rate reported in an audit of UK practice (Gavin 2013). The EAC retained the assumption that the proportion of successful colonoscopies with Endocuff vision was 0.1% lower (92.2%) in accordance with the ADENOMA trial findings (Ngu 2018). In this subgroup, Endocuff Vision was associated with a cost increase of £16.92. In sensitivity analysis for this subgroup in which UK data from Sagar (2015) was applied to the stage distribution of screen detected and symptomatic CRC, the cost increase attributable to Endocuff Vision fell modestly to £16.21. The cost increases reflect the very modest gain in ADR for Endocuff Vision in this population.

Model validation

The EAC accepted the structure of the cost model submitted by the sponsor. The EAC notes that the sponsor's model is adapted from a previous model of the CRC pathway. This is a very complex model increasing the potential for errors. The EAC corrected some minor errors and made changes to two parameters. Mostly, the impact of these changes was small. However, the use of UK data on the stage distribution of screen detected and symptomatic CRC had a large impact, generating larger savings for Endocuff Vision than those estimated using the German data in the sponsor's model.

4.5 EAC Interpretation of economic evidence

The EAC assessed the sponsor's model and found the structure to be acceptable. The EAC believes the Markov model is of appropriate complexity to sufficiently estimate the impact of changes in the ADR on subsequent CRC treatment costs. The EAC considers the sponsor's data sources for the parameterization of the model to be broadly acceptable. The EAC made amendments to two parameter sources in the model. It also amended some minor errors in the parameterization of the model. The EAC notes that the use of German data to estimate the difference in the stage distribution of screen detected and symptomatic CRC generates conservative estimates of the overall cost impact of Endocuff Vision . The EAC substituted this data with data from the UK which generates larger savings with Endocuff Vision. Hence the EAC supports the sponsor's conclusion that Endocuff Vision is likely to save money when used as part of the BCSP.

The EAC notes that the findings are sensitive to the magnitude of the difference in ADR between colonoscopy with and without Endocuff Vision. A gain in ADR of at least 3.0% is required for Endocuff Vision to be cost neutral in the BCSP. This is below the lower limit of the confidence interval for the difference reported in the ADENOMA trial (Ngu et al. 2018), and hence Endocuff Vision is likely to be cost saving when used within the BCSP. However, this finding would suggest that Endocuff Vision may not be cost saving beyond the BCSP where the evidence for an improvement in the ADR is limited.

Impact on the cost difference between the technology and comparator of additional clinical and economic analyses undertaken by the External Assessment Centre

The EAC amended the sponsor's cost analysis. The most significant changes were those relating to the stage distribution of screen detected and symptomatic CRC which the EAC chose to parameterize from UK data relating to the BCSP. The impact of this change was to increase the cost saving attributable to Endocuff Vision. This, in turn, indicated that Endocuff Vision was cost neutral at a much lower improvement in ADR (3.0%) than that estimated by the sponsor (8.5%). Notably, this value is below the one sided 95% CI for the ADR gain with Endocuff Vision reported by the ADENOMA trial (Ngu 2018). However, the inference that Endocuff Vision is cost saving remained sensitive to estimates of the magnitude of the saving in treatment costs associated with detection of CRC at an earlier stage.

The sponsor did not submit an analysis of the cost impact of Endocuff Vision in a non-BCSP population. Data from ADENOMA (Ngu 2018) indicates that this population is likely to have a lower adenoma rate. In such a population

the scope for Endocuff Vision to offset increased screen costs through improved ADR is lower. The EAC undertook a subgroup analysis in which this population was modelled. It applied the gain in ADR for Endocuff Vision observed in the ADENOMA trial for non-BCSP patients. This gain was marginal (0.4%) and the analysis indicated that Endocuff Vision is not cost saving in this population.

5 Conclusions

5.1 Conclusions on the clinical evidence

The sponsor included in their submission all available evidence on EV as specified by the scope. This consisted from 2 RCTs (ADENOMA, E-Cap) and 2 non-RCTs (Rameshshanker 2016, Tsiamoulos 2018), all comparing EVC with standard colonoscopy.

Given the limitations surrounding the rest of the evidence, the superiority of EVC in comparison with SC is supported mainly by a good quality, multi-centre, national RCT (ADENOMA) that shows that in a BCSP population the use of EVC increases ADR by 10.8%. The EAC considered that this multi-centre RCT, which is representative of UK practice, was subject to overall low risk of bias and that the comparative benefit was mainly attributable to EVC.

Given the association between colonoscopists' expertise and ADR increase with EVC, it is likely that EVC will not lead in an increase in ADR in centres with high expertise and high baseline ADR rates.

5.2 Conclusions on the economic evidence

The EAC agrees with the sponsor's conclusion that the use of Endocuff Vision as part of the BCSP is likely to be cost saving. The EAC conducted subgroup analysis for a non-BCSP population and concluded that Endocuff Vision is unlikely to be cost saving for this population.

6 Summary of the combined clinical and economic sections

An improvement in ADR above 3.0% is sufficient to generate cost savings through reduced CRC treatment costs which offset the additional costs of using the device in the BCSP. Data from the ADENOMA trial (Ngu 2018) indicates that an improvement in ADR of 5.1% or more attributable to the use of EV in the BCSP is likely. The use of EVC results in higher ADR rates when used in a BCSP population and by less experienced colonoscopists. Evidence from the ADENOMA trial suggests that Endocuff Vision is unlikely to save costs in non-BCSP populations.

7 Implications for research

Given the influence of endoscopic experience on ADR future comparative studies should be multi-centre national RCTs adequately powered to detect a decrease in the rate of interval CRC with EVC.

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Appendix A: Search strategies

Total records retrieved: 474

Total following de-duplication: 313

- Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
- Search date: 4th July 2018

1	(endocuff$ or endo-cuff$ or ecvision$ or ec-vision$).ti,ab,kf.	39
2	ec-assisted.ti,ab,kf.	5
3	(aec110 or aec120 or aec130 or aec140).ti,ab,kf.	0
4	(aec-110 or aec-120 or aec-130 or aec-140).ti,ab,kf.	0
5	(arc medical$ or arcmedical$ or arc design$ or arcdesign$ or norgine$).ti,ab,kf,in.	46
6	or/1-5	83
7	Endoscopes, Gastrointestinal/	1638
8	exp Colonoscopes/	1263
9	Endoscopy, Gastrointestinal/	17082
10	exp Colonoscopy/	27083
11	exp Colorectal Neoplasms/	181324
12	Colonic Polyps/	7647
13	(colonoscop$ or endoscop$ or sigmoidoscop$).ti,ab,kf.	205105
14	((bowel$1 or intestin$ or colorectal$ or colon$ or rectum$ or rectal$ or anal$ or anus or sigmoid$) adj3 (screen$ or investigat$ or diagnos$ or detect$)).ti,ab,kf.	149690
15	((bowel$1 or intestin$ or colorectal$ or colon$ or rectum$ or rectal$ or anal$ or anus or sigmoid$) adj3 (cancer$ or neoplasm$ or tumor$ or tumour$ or malignan$ or carcin$ or polyp$ or oncolog$ or sarcoma$ or adenocarcin$)).ti,ab,kf.	296223
16	or/7-15	641471

17	((plastic$ or flexib$ or retract$ or stretch$ or soft or novel) adj5 (tip or tips or cuff or cuffs or cap or caps or attachment$ or accessor$ or device$1 or hinge$1)).ti,ab,kf.	16895
18	((plastic$ or flexib$ or retract$ or stretch$ or invert$ or evert$ or soft or hinge$1) adj5 (finger$1 or branch$ or arm or arms or projection$1 or flange$1)).ti,ab,kf.	3200
19	((assisted or assistive) adj5 (tip or tips or cuff or cuffs or cap or caps or attachment$ or accessor$ or device$1)).ti,ab,kf.	4257
20	or/17-19	24115
21	16 and 20	1154
22	((colonoscop$ or endoscop$ or sigmoidoscop$) and (tip or tips or cuff or cuffs or cap or caps or attachment$ or accessor$)).ti.	444
23	((colonoscop$ or endoscop$ or sigmoidoscop$) adj5 (tip or tips or cuff or cuffs or cap or caps or attachment$ or accessor$)).ab,kf.	1056
24	6 or 21 or 22 or 23	2341
25	exp animals/ not humans/	4468922
26	24 not 25	2150
27	limit 26 to yr="2018 -Current"	108
28	from 27 keep 1-108	108

- Embase 1974 to 2018 Week 27
- Search date: 4th July 2018

1	(endocuff$ or endo-cuff$ or ecvision$ or ec-vision$).ti,ab,kw,dv.	103
2	ec-assisted.ti,ab,kw,dv.	12
3	(aec110 or aec120 or aec130 or aec140).ti,ab,kw,dv.	3
4	(aec-110 or aec-120 or aec-130 or aec-140).ti,ab,kw,dv.	0
5	(arc medical$ or arcmedical$ or arc design$ or arcdesign$ or norgine$).ti,ab,kw,in,dm.	245
6	or/1-5	328

7	digestive endoscope/	941
8	exp sigmoidoscope/	318
9	exp colonoscope/	2982
10	gastrointestinal endoscopy/	29696
11	colonoscopy/	67327
12	sigmoidoscopy/	11445
13	exp rectum tumor/	219464
14	exp colon tumor/	281974
15	exp colon polyp/	18212
16	(colonoscop$ or endoscop$ or sigmoidoscop$).ti,ab,kw.	318538
17	((bowel$1 or intestin$ or colorectal$ or colon$ or rectum$ or rectal$ or anal$ or anus or sigmoid$) adj3 (screen$ or investigat$ or diagnos$ or detect$)).ti,ab,kw.	208910
18	((bowel$1 or intestin$ or colorectal$ or colon$ or rectum$ or rectal$ or anal$ or anus or sigmoid$) adj3 (cancer$ or neoplasm$ or tumor$ or tumour$ or malignan$ or carcin$ or polyp$ or oncolog$ or sarcoma$ or adenocarcin$)).ti,ab,kw.	419944
19	or/7-18	952437
20	((plastic$ or flexib$ or retract$ or stretch$ or soft or novel) adj5 (tip or tips or cuff or cuffs or cap or caps or attachment$ or accessor$ or device$1 or hinge$1)).ti,ab,kw.	19376
21	((plastic$ or flexib$ or retract$ or stretch$ or invert$ or evert$ or soft or hinge$1) adj5 (finger$1 or branch$ or arm or arms or projection$1 or flange$1)).ti,ab,kw.	3790
22	((assisted or assistive) adj5 (tip or tips or cuff or cuffs or cap or caps or attachment$ or accessor$ or device$1)).ti,ab,kw.	6061
23	or/20-22	28874
24	19 and 23	2273
25	((colonoscop$ or endoscop$ or sigmoidoscop$) and (tip or tips or cuff or cuffs or cap or caps or attachment$ or accessor$)).ti.	681

26	((colonoscop$ or endoscop$ or sigmoidoscop$) adj5 (tip or tips or cuff or cuffs or cap or caps or attachment$ or accessor$)).ab,kw.	1979
27	6 or 24 or 25 or 26	4445
28	(animal/ or animal experiment/ or animal model/ or animal tissue/ or nonhuman/) not exp human/	5918549
29	27 not 28	4121
30	limit 29 to yr="2018 -Current"	124

- EconLit (Proquest)
- Search date: 4th July 2018

Set#	Searched for	Databases	Results
S1	endocuff* or endo-cuff* or ecvision* or ec-vision*	EconLit	1
S2	ec-assisted	EconLit	0
S3	aec110 or aec120 or aec130 or aec140	EconLit	0
S4	aec-110 or aec-120 or aec-130 or aec-140	EconLit	0
S5	"arc medical*" or arcmedical* or "arc design*" or arcdesign* or norgine*	EconLit	1
S6	(endocuff* or endo-cuff* or ecvision* or ec-vision*) OR ec-assisted OR (aec110 or aec120 or aec130 or aec140) OR (aec-110 or aec-120 or aec-130 or aec-140) OR ("arc medical*" or arcmedical* or "arc design*" or arcdesign* or norgine*)	EconLit These databases are searched for part of your query.	2
S7	colonoscop* or endoscop* or sigmoidoscop*	EconLit	45
S8	((bowel* or intestin* or colorectal* or colon* or rectum* or rectal* or anal* or anus or sigmoid*) N/3 (screen* or investigat* or diagnos* or detect*))	EconLit	2382
S9	((bowel* or intestin* or colorectal* or colon* or rectum* or rectal* or	EconLit	188

	anal* or anus or sigmoid*) N/3 (cancer* or neoplasm* or tumor* or tumour* or malignan* or carcin* or polyp* or oncolog* or sarcoma* or adenocarcin*))		
S10	(colonoscop* or endoscop* or sigmoidoscop*) OR ((bowel* or intestin* or colorectal* or colon* or rectum* or rectal* or anal* or anus or sigmoid*) N/3 (screen* or investigat* or diagnos* or detect*)) OR ((bowel* or intestin* or colorectal* or colon* or rectum* or rectal* or anal* or anus or sigmoid*) N/3 (cancer* or neoplasm* or tumor* or tumour* or malignan* or carcin* or polyp* or oncolog* or sarcoma* or adenocarcin*))	EconLit These databases are searched for part of your query.	2542
S11	((plastic* or flexib* or retract* or stretch* or soft or novel) N/5 (tip or tips or cuff or cuffs or cap or caps or attachment* or accessor* or device* or hinge*))	EconLit	82
S12	((plastic* or flexib* or retract* or stretch* or invert* or evert* or soft or hinge*) N/5 (finger* or branch* or arm or arms or projection* or flange*))	EconLit	27
S13	((assisted or assistive) N/5 (tip or tips or cuff or cuffs or cap or caps or attachment* or accessor* or device*))	EconLit	15
S14	((plastic* or flexib* or retract* or stretch* or soft or novel) N/5 (tip or tips or cuff or cuffs or cap or caps or attachment* or accessor* or device* or hinge*)) OR ((plastic* or flexib* or retract* or stretch* or invert* or evert* or soft or hinge*) N/5 (finger* or branch* or arm or arms or projection* or flange*)) OR ((assisted or assistive) N/5 (tip or tips or cuff or cuffs or cap or caps or attachment* or accessor* or device*))	EconLit These databases are searched for part of your query.	123
S15	((colonoscop* or endoscop* or sigmoidoscop*) OR ((bowel* or intestin* or colorectal* or colon* or	EconLit	0

	rectum* or rectal* or anal* or anus or sigmoid*) N/3 (screen* or investigat* or diagnos* or detect*)) OR ((bowel* or intestin* or colorectal* or colon* or rectum* or rectal* or anal* or anus or sigmoid*) N/3 (cancer* or neoplasm* or tumor* or tumour* or malignan* or carcin* or polyp* or oncolog* or sarcoma* or adenocarcin*))) AND (((plastic* or flexib* or retract* or stretch* or soft or novel) N/5 (tip or tips or cuff or cuffs or cap or caps or attachment* or accessor* or device* or hinge*)) OR ((plastic* or flexib* or retract* or stretch* or invert* or evert* or soft or hinge*) N/5 (finger* or branch* or arm or arms or projection* or flange*)) OR ((assisted or assistive) N/5 (tip or tips or cuff or cuffs or cap or caps or attachment* or accessor* or device*)))	These databases are searched for part of your query.	
S16	ti(((colonoscop* or endoscop* or sigmoidoscop*) and (tip or tips or cuff or cuffs or cap or caps or attachment* or accessor*)))	EconLit	0
S17	ab(((colonoscop* OR endoscop* OR sigmoidoscop*) N/5 (tip OR tips OR cuff OR cuffs OR cap OR caps OR attachment* OR accessor*)))	EconLit	0
S18	((endocuff* or endo-cuff* or ecvision* or ec-vision*) OR ec-assisted OR (aec110 or aec120 or aec130 or aec140) OR (aec-110 or aec-120 or aec-130 or aec-140) OR ("arc medical*" or arcmedical* or "arc design*" or arcdesign* or norgine*)) OR (((colonoscop* or endoscop* or sigmoidoscop*) OR ((bowel* or intestin* or colorectal* or colon* or rectum* or rectal* or anal* or anus or sigmoid*) N/3 (screen* or investigat* or diagnos* or detect*)) OR ((bowel* or intestin* or colorectal* or colon* or rectum* or rectal* or anal* or anus or sigmoid*) N/3 (cancer* or neoplasm* or tumor* or tumour* or malignan* or carcin* or polyp* or	EconLit These databases are searched for part of your query.	2

	oncolog* or sarcoma* or adenocarcin*))) AND (((plastic* or flexib* or retract* or stretch* or soft or novel) N/5 (tip or tips or cuff or cuffs or cap or caps or attachment* or accessor* or device* or hinge*)) OR ((plastic* or flexib* or retract* or stretch* or invert* or evert* or soft or hinge*) N/5 (finger* or branch* or arm or arms or projection* or flange*)) OR ((assisted or assistive) N/5 (tip or tips or cuff or cuffs or cap or caps or attachment* or accessor* or device*))))) OR ti(((colonoscop* OR endoscop* OR sigmoidoscop*) AND (tip OR tips OR cuff OR cuffs OR cap OR caps OR attachment* OR accessor*))) OR ab(((colonoscop* OR endoscop* OR sigmoidoscop*) NEAR/5 (tip OR tips OR cuff OR cuffs OR cap OR caps OR attachment* OR accessor*)))		
S19	(((endocuff* or endo-cuff* or ecvision* or ec-vision*) OR ec-assisted OR (aec110 or aec120 or aec130 or aec140) OR (aec-110 or aec-120 or aec-130 or aec-140) OR ("arc medical*" or arcmedical* or "arc design*" or arcdesign* or norgine*)) OR (((colonoscop* or endoscop* or sigmoidoscop*) OR ((bowel* or intestin* or colorectal* or colon* or rectum* or rectal* or anal* or anus or sigmoid*) N/3 (screen* or investigat* or diagnos* or detect*)) OR ((bowel* or intestin* or colorectal* or colon* or rectum* or rectal* or anal* or anus or sigmoid*) N/3 (cancer* or neoplasm* or tumor* or tumour* or malignan* or carcin* or polyp* or oncolog* or sarcoma* or adenocarcin*))) AND (((plastic* or flexib* or retract* or stretch* or soft or novel) N/5 (tip or tips or cuff or cuffs or cap or caps or attachment* or accessor* or device* or hinge*)) OR ((plastic* or flexib* or retract* or stretch* or invert* or evert* or soft or hinge*) N/5 (finger* or branch* or arm or	EconLit These databases are searched for part of your query.	0

	arms or projection* or flange*)) OR ((assisted or assistive) N/5 (tip or tips or cuff or cuffs or cap or caps or attachment* or accessor* or device*)))) OR ti(((colonoscop* OR endoscop* OR sigmoidoscop*) AND (tip OR tips OR cuff OR cuffs OR cap OR caps OR attachment* OR accessor*))) OR ab(((colonoscop* OR endoscop* OR sigmoidoscop*) NEAR/5 (tip OR tips OR cuff OR cuffs OR cap OR caps OR attachment* OR accessor*)))) AND pd(20180101-20191231)		

- CDSR
- Search date: 4th July 2018

ID	Search	Hits
#1	(endocuff* or endo-cuff* or ecvision* or ec-vision*):ti,ab,kw	51
#2	ec-assisted:ti,ab,kw	5
#3	(aec110 or aec120 or aec130 or aec140):ti,ab,kw	0
#4	(aec-110 or aec-120 or aec-130 or aec-140):ti,ab,kw	0
#5	(arc next medical* or arcmedical* or arc next design* or arcdesign* or norgine*):ti,ab,kw	15
#6	#1 or #2 or #3 or #4 or #5	60
#7	[mh ^"Endoscopes, Gastrointestinal"]	65
#8	[mh Colonoscopes]	140
#9	[mh ^"Endoscopy, Gastrointestinal"]	906
#10	[mh Colonoscopy]	2069
#11	[mh "Colorectal Neoplasms"]	8199
#12	[mh ^"Colonic Polyps"]	438
#13	(colonoscop* or endoscop* or sigmoidoscop*):ti,ab,kw	23390
#14	((bowel* or intestin* or colorectal* or colon* or rectum* or rectal* or anal* or anus or sigmoid*) near/3 (screen* or investigat* or diagnos* or detect*)):ti,ab,kw	15447
#15	((bowel* or intestin* or colorectal* or colon* or rectum* or rectal* or anal* or anus or sigmoid*) near/3 (cancer* or neoplasm* or tumor* or tumour* or malignan* or carcin* or polyp* or oncolog* or sarcoma* or adenocarcin*)):ti,ab,kw	27883
#16	#7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15	58843
#17	((plastic* or flexib* or retract* or stretch* or soft or novel) near/5 (tip or tips or cuff or cuffs or cap or caps or attachment* or accessor* or device* or hinge*)):ti,ab,kw	1292

#18	((plastic* or flexib* or retract* or stretch* or invert* or evert* or soft or hinge*) near/5 (finger* or branch* or arm or arms or projection* or flange*)):ti,ab,kw	246
#19	((assisted or assistive) near/5 (tip or tips or cuff or cuffs or cap or caps or attachment* or accessor* or device*)):ti,ab,kw	631
#20	#17 or #18 or #19	2122
#21	#16 and #20	251
#22	((colonoscop* or endoscop* or sigmoidoscop*) and (tip or tips or cuff or cuffs or cap or caps or attachment* or accessor*)):ti	143
#23	((colonoscop* or endoscop* or sigmoidoscop*) near/5 (tip or tips or cuff or cuffs or cap or caps or attachment* or accessor*)):ab,kw	210
#24	#6 or #21 or #22 or #23 Publication Year from 2018, in Cochrane Reviews (Reviews and Protocols)	0

- CENTRAL
- Search date: 4th July 2018

ID	Search	Hits
#1	(endocuff* or endo-cuff* or ecvision* or ec-vision*)	53
#2	ec-assisted	5
#3	(aec110 or aec120 or aec130 or aec140)	0
#4	(aec-110 or aec-120 or aec-130 or aec-140)	0
#5	(arc next medical* or arcmedical* or arc next design* or arcdesign* or norgine*)	62
#6	#1 or #2 or #3 or #4 or #5	109
#7	[mh ^"Endoscopes, Gastrointestinal"]	65
#8	[mh Colonoscopes]	140
#9	[mh ^"Endoscopy, Gastrointestinal"]	906
#10	[mh Colonoscopy]	2069
#11	[mh "Colorectal Neoplasms"]	8199
#12	[mh ^"Colonic Polyps"]	438
#13	(colonoscop* or endoscop* or sigmoidoscop*)	27058
#14	((bowel* or intestin* or colorectal* or colon* or rectum* or rectal* or anal* or anus or sigmoid*) near/3 (screen* or investigat* or diagnos* or detect*))	24602
#15	((bowel* or intestin* or colorectal* or colon* or rectum* or rectal* or anal* or anus or sigmoid*) near/3 (cancer* or neoplasm* or tumor* or tumour* or malignan* or carcin* or polyp* or oncolog* or sarcoma* or adenocarcin*))	29297
#16	#7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15	70663
#17	((plastic* or flexib* or retract* or stretch* or soft or novel) near/5 (tip or tips or cuff or cuffs or cap or caps or attachment* or accessor* or device* or hinge*))	1427
#18	((plastic* or flexib* or retract* or stretch* or invert* or evert* or soft or hinge*) near/5 (finger* or branch* or arm or arms or projection* or flange*))	338
#19	((assisted or assistive) near/5 (tip or tips or cuff or cuffs or cap or caps or attachment* or accessor* or device*))	809

#20	#17 or #18 or #19	2492
#21	#16 and #20	516
#22	((colonoscop* or endoscop* or sigmoidoscop*) and (tip or tips or cuff or cuffs or cap or caps or attachment* or accessor*))	781
#23	((colonoscop* or endoscop* or sigmoidoscop*) near/5 (tip or tips or cuff or cuffs or cap or caps or attachment* or accessor*))	282
#24	#6 or #21 or #22 or #23 Publication Year from 2018, in Trials	27

- HTA
- Search date: 4th July 2018

ID	Search	Hits
#1	(endocuff* or endo-cuff* or ecvision* or ec-vision*)	53
#2	ec-assisted	5
#3	(aec110 or aec120 or aec130 or aec140)	0
#4	(aec-110 or aec-120 or aec-130 or aec-140)	0
#5	(arc next medical* or arcmedical* or arc next design* or arcdesign* or norgine*)	62
#6	#1 or #2 or #3 or #4 or #5	109
#7	[mh ^"Endoscopes, Gastrointestinal"]	65
#8	[mh Colonoscopes]	140
#9	[mh ^"Endoscopy, Gastrointestinal"]	906
#10	[mh Colonoscopy]	2069
#11	[mh "Colorectal Neoplasms"]	8199
#12	[mh ^"Colonic Polyps"]	438
#13	(colonoscop* or endoscop* or sigmoidoscop*)	27058
#14	((bowel* or intestin* or colorectal* or colon* or rectum* or rectal* or anal* or anus or sigmoid*) near/3 (screen* or investigat* or diagnos* or detect*))	24602
#15	((bowel* or intestin* or colorectal* or colon* or rectum* or rectal* or anal* or anus or sigmoid*) near/3 (cancer* or neoplasm* or tumor* or tumour* or malignan* or carcin* or polyp* or oncolog* or sarcoma* or adenocarcin*))	29297
#16	#7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15	70663
#17	((plastic* or flexib* or retract* or stretch* or soft or novel) near/5 (tip or tips or cuff or cuffs or cap or caps or attachment* or accessor* or device* or hinge*))	1427
#18	((plastic* or flexib* or retract* or stretch* or invert* or evert* or soft or hinge*) near/5 (finger* or branch* or arm or arms or projection* or flange*))	338
#19	((assisted or assistive) near/5 (tip or tips or cuff or cuffs or cap or caps or attachment* or accessor* or device*))	809
#20	#17 or #18 or #19	2492
#21	#16 and #20	516
#22	((colonoscop* or endoscop* or sigmoidoscop*) and (tip or tips or cuff or cuffs or cap or caps or attachment* or accessor*))	781
#23	((colonoscop* or endoscop* or sigmoidoscop*) near/5 (tip or tips or cuff or cuffs or cap or caps or attachment* or accessor*))	282

#24	#6 or #21 or #22 or #23 Publication Year from 2018, in Technology Assessments	0

- Web of Science
- Search date: 4th July 2018

# 18	183	#6 OR #15 OR #16 OR #17 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2018
# 17	49	TS=((colonoscop* OR endoscop* OR sigmoidoscop*) NEAR/5 ("tip" OR "tips" OR "cuff" OR "cuffs" OR "cap" OR "caps" OR attachment* OR accessor*)) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2018
# 16	34	TI=((colonoscop* OR endoscop* OR sigmoidoscop*) AND ("tip" OR "tips" OR "cuff" OR "cuffs" OR "cap" OR "caps" OR attachment* OR accessor*)) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2018
# 15	101	#10 AND #14 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2018
# 14	2,780	#11 OR #12 OR #13 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2018
# 13	300	TS=(("assisted" OR "assistive") NEAR/5 ("tip" OR "tips" OR "cuff" OR "cuffs" OR "cap" OR "caps" OR attachment* OR accessor* OR device$)) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2018
# 12	202	TS=((plastic* OR flexib* OR retract* OR stretch* OR invert* OR evert* OR "soft" OR hinge$) NEAR/5 (finger$ OR branch* OR "arm" OR "arms" OR projection$ OR flange$)) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2018
# 11	2,307	TS=((plastic* OR flexib* OR retract* OR stretch* OR "soft" OR "novel") NEAR/5 ("tip" OR "tips" OR "cuff" OR "cuffs" OR "cap"

		OR "caps" OR attachment* OR accessor* OR device$ OR hinge$)) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2018
# 10	28,952	#7 OR #8 OR #9 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2018
# 9	13,098	TS=((bowel$ OR intestin* OR colorectal* OR colon* OR rectum* OR rectal* OR anal* OR "anus" OR sigmoid*) NEAR/3 (cancer* OR neoplasm* OR tumor* OR tumour* OR malignan* OR carcin* OR polyp* OR oncolog* OR sarcoma* OR adenocarcin*)) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2018
# 8	11,772	TS=((bowel$ OR intestin* OR colorectal* OR colon* OR rectum* OR rectal* OR anal* OR "anus" OR sigmoid*) NEAR/3 (screen* OR investigat* OR diagnos* OR detect*)) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2018
# 7	6,424	TS=(colonoscop* OR endoscop* OR sigmoidoscop*) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2018
# 6	48	#1 OR #2 OR #3 OR #4 OR #5 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2018
# 5	35	OG=(arc NEAR/0 medical* OR arcmedical* OR arc NEAR/0 design* OR arcdesign* OR norgine*) OR AD=(arc NEAR/0 medical* OR arcmedical* OR arc NEAR/0 design* OR arcdesign* OR norgine*) OR SG=(arc NEAR/0 medical* OR arcmedical* OR arc NEAR/0 design* OR arcdesign* or norgine*) OR FO=(arc NEAR/0 medical* OR arcmedical* OR arc NEAR/0 design* OR arcdesign* OR norgine*) OR TS=(arc NEAR/0 medical* OR arcmedical* OR arc NEAR/0 design* OR arcdesign* OR norgine*) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2018
# 4	0	TS=("aec-110" OR "aec-120" OR "aec-130" OR "aec-140")

		Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2018
# 3	0	TS=("aec110" OR "aec120" OR "aec130" OR "aec140") Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2018
# 2	1	TS="ec-assisted" Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2018
# 1	13	TS=(endocuff* or endo-cuff* or ecvision* or ec-vision*) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2018

- WHO ICTRP
- Search date: 4th July 2018

Default search screen: **endocuff OR endo-cuff OR ecvision OR ec-vision OR ec-assisted OR aec110 OR aec120 OR aec130 OR aec140 OR aec-110 OR aec-120 OR aec-130 OR aec-140** – limited to 2018, 4 results

- ClinicalTrials.gov
- Search date: 4th July 2018

Expert search: **endocuff OR endo-cuff OR ecvision OR ec-vision OR ec-assisted OR aec110 OR aec120 OR aec130 OR aec140 OR aec-110 OR aec-120 OR aec-130 OR aec-140** – limited to 2018, 4 results

- UK Clinical Trials Gateway
- Search date: 5th July 2018

Limited to 2018 only:

endocuff*: 0 results

endo-cuff*: 0 results

ecvision*: 0 results

ec-vision*: 0 results

ec-assisted*: 0 results

aec110*: 0 results

aec120*: 0 results

aec130*: 0 results

aec140*: 0 results

aec-110*: 0 results

aec-120*: 0 results

aec-130*: 0 results

aec-140*: 0 results

- Cost Effectiveness Analysis Registry (CEA Registry)
- Search date: 5th July 2018

endocuff: no results

endo-cuff: no results

ecvision no results

ec-vision: no results

aec110: no results

aec120: no results

aec130: no results

aec140: no results

aec-110: no results

aec-120: no results

aec-130: no results

aec-140: no results

- FDA
- Search date: 5th July 2018

Limited to 2018 only:

endocuff: no results

endo-cuff: no results

ecvision no results

ec-vision: no results

aec110: no results

aec120: no results

aec130: no results

aec140: no results

aec-110: no results

aec-120: no results

aec-130: no results

aec-140: no results

- Digestive Disease Week 2018
- Search date: 5th July 2018

http://www.ddw.org/ddwwebsite/education/abstracts

endocuff: 2 results

"endo-cuff": 0 results

ecvision: 0 results

"ec-vision": 0 results

"ec-assisted": 0 results

aec110: 0 results

aec120: 0 results

aec130: 0 results

aec140: 0 results

"aec-110": 0 results

"aec-120": 0 results

"aec-130": 0 results

"aec-140": 0 results

Search within issue: https://www.gastrojournal.org/issue/S0016-5085(18)X6001-6
(Gastroenterology, May 2018 Volume 154, Issue 6, Supplement 1, S-1-S-1372)

endocuff: 11 results

"endo-cuff": 0 results

ecvision: 0 results

"ec-vision": 0 results

"ec-assisted": 0 results

aec110: 0 results

aec120: 0 results

aec130: 0 results

aec140: 0 results

"aec-110": 0 results

"aec-120": 0 results

"aec-130": 0 results

"aec-140": 0 results

Search within issue: https://www.giejournal.org/issue/S0016-5107(18)X0005-4

(Gastrointestinal Endoscopy, June 2018 Volume 87, Issue 6, Supplement, AB1-AB668)

endocuff: 9 results

"endo-cuff": 0 results

ecvision: 0 results

"ec-vision": 0 results

"ec-assisted": 0 results

aec110: 0 results

aec120: 0 results

aec130: 0 results

aec140: 0 results

"aec-110": 0 results

"aec-120": 0 results

"aec-130": 0 results

"aec-140": 0 results

- American College of Gastroenterology Annual Scientific Meeting 2018
- not happened yet (as of 5th July 2018)

- British Society of Gastroenterology Annual Meeting 2018
- Search date: 5th July 2018

Search within issue: https://gut.bmj.com/content/67/Suppl_1 (Gut, June 2018 - Volume 67 - Suppl 1)

endocuff: 2 results

"endo-cuff": 0 results

ecvision: 0 results

"ec-vision": 0 results

"ec-assisted": 0 results

aec110: 0 results

aec120: 0 results

aec130: 0 results

aec140: 0 results

"aec-110": 0 results

"aec-120": 0 results

"aec-130": 0 results

"aec-140": 0 results

- United European Gastroenterology Week 2018
- not happened yet (as of 5th July 2018)

Appendix B: Methodological quality template

Study identification Include author, title, reference, year of publication					
Guideline topic:	**Review question no:**				
Checklist completed by:					
		Circle or highlight one option for each question			
A. Selection bias (systematic differences between the comparison groups)					
A1	An appropriate method of randomisation was used to allocate participants to treatment groups (which would have balanced any confounding factors equally across groups)	Yes	No	Unclear	N/A
A2	There was adequate concealment of allocation (such that investigators, clinicians and participants cannot influence enrolment or treatment allocation)	Yes	No	Unclear	N/A
A3	The groups were comparable at baseline, including all major confounding and prognostic factors (patient characteristics)	Yes	No	Unclear	N/A
A4	Are the patient inclusion/exclusion criteria clearly defined?	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was selection bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect: .					

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B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)					
B1	The comparison groups received the same care apart from the intervention(s) studied	Yes	No	Unclear	N/A
B2	Participants receiving care were kept 'blind' to treatment allocation	Yes	No	Unclear	N/A
B3	Individuals administering care were kept 'blind' to treatment allocation	Yes	No	Unclear	N/A

Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?

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Low risk of bias	Unclear/unknown risk	High risk of bias

Likely direction of effect:

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C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)					
C1	All groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up)	Yes	No	Unclear	N/A
C2	a. How many participants did not complete treatment in each group?				

	b. The groups were comparable for treatment completion (that is, there were no important or systematic differences between groups in terms of those who did not complete treatment)	Yes	No	Unclear	N/A
C3	a. For how many participants in each group were no outcome data available?				
	b. The groups were comparable with respect to the availability of outcome data (that is, there were no important or systematic differences between groups in terms of those for whom outcome data were not available).	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					
D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)					
D1	The study had an appropriate length of follow-up	Yes	No	Unclear	N/A

D2	The study used a precise definition of outcome	Yes	No	Unclear	N/A
D3	A valid and reliable method was used to determine the outcome	Yes	No	Unclear	N/A
D4	Investigators were kept 'blind' to participants' exposure to the intervention	Yes	No	Unclear	N/A
D5	Investigators were kept 'blind' to other important confounding and prognostic factors	Yes	No	Unclear	N/A

Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?

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Low risk of bias	Unclear/unknown risk	High risk of bias

Likely direction of effect:

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D. Other

D1	Does the trial have any disclosures of potential conflicts of interest?	Yes	No	Unclear	N/A
D2	Is the study multi-centre?	Yes	No	Unclear	N/A

D3	Is there a sample size calculation for the primary endpoint?	Yes	No	Unclear	N/A
D4	Did the study used ADR as the primary endpoint?	Yes	No	Unclear	N/A

Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?

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Low risk of bias	Unclear/unknown risk	High risk of bias

Likely direction of effect:

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Appendix C: Compatibility schedule

ENDOCUFF-VISION-Compatibility-Schedu

Appendix D: Updated literature search November 2018

All searches were re-run unchanged (see Appendix A for the original searches undertaken for the assessment report), with the following exceptions:

- The HTA database was not search as this is now closed to new records
- British Society of Gastroenterology Annual Meeting 2018 and Digestive Disease Week 2018 were not searched for abstracts because the meetings were already covered in the original search

Results were then de-duplicated against the results found in the original search.
The numbers of results of this re-run search (pre-deduplication) are summarised in the following table. All searches were carried out on the 14th of November 2018.

DATABASE	RESULTS
Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present	168
Embase 1974 to 2018 Week 46	269
EconLit (Proquest)	0
CDSR	5
CENTRAL	49
Web of Science	297
WHOICTRP	6
ClinicalTrials.gov	5
UK Clinical Trials gateway	0
CEA Registry	0
FDA	0
United European Gastroenterology Week 2018*	5
American College of Gastroenterology Annual Scientific Meeting 2018*	1
TOTAL PRE-DEDUPLICATION	805
** not searched in the original search because the 2018 meeting had not taken place at that time*	

Following de-duplication, 225 new records were found. Following an initial review of the titles and abstracts, 205 records were excluded, leaving 20 records (18 studies and 2 records of ongoing studies).
Following a full-text review of the studies, 3 relevant records were retained. Only 1 study referred to Endocuff Vision, while the other 2 contained outcomes relevant to the question of colonoscopist experience and the benefit of Endocuff with varying baseline levels of ADR.

More specifically, more evidence on Endocuff Vision is provided by Varma 2018. This is an abstract reporting the preliminary analysis of a prospective, single centre, non-randomised, comparative study in 105 adults aged >50 years undergoing screening/diagnostic colonoscopy comparing Endocuff Vision with standard colonoscopy and Cap-assisted colonoscopy (Olympus).

After excluding 21 patients, there were 37 patients in the SC group, 11 in the Olympus Cap group, and 36 in the Endocuff Vision group. The ADR rates were similar between the 3 groups. This is a preliminary analysis of a single centre non-randomised study and the additional evidence do not significant value to the decision issue.

Two more abstracts (Clelia 2018, Geyer 2018) provided additional information on the impact of baseline ADR rates in the efficacy of Endocuff. First Clelia 2018, reported a network meta-analysis, on the efficacy of mucosal flattening assisted colonoscopy vs standard colonoscopy to improve the adenoma detection rate in patients undergoing colonoscopy. A total of 6407 patients (Endocuff 2986, EndoRing 354 and Standard 3067) from 10 studies were included. The authors concluded that Endocuff devices improve ADR overall by 1.33 - 1.34 both on per protocol and by intention to treat analysis. The improvement was not significant when the ADR was greater than 40% using standard colonoscopy. Endocuff was clinically and statistically relevant when ADR with standard colonoscopy is lower than 25%. (OR: 1.87 in ITT analysis). Geyer 2018 reported their preliminary analysis of a single centre, RCT comparing 2849 patients who underwent ambulant with SC or full-spectrum colonoscopy (FUSE) or Endocuff-assisted colonoscopy. The ADR rates were 50% for FUSE, 54% for SC and 47% for Endocuff ($p>0.5$). As a result the authors concluded that neither Endocuff nor FUSE significantly increased the ADR and if the baseline ADR is close to 50% no further benefit can be expected from these additional technologies.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology guidance

Assessment report overview

Endocuff Vision for endoscopic investigation

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 overview also contains:

1 The technology

Endocuff Vision (Norgine) is a single-use device which fits over the end of most conventional colonoscopes and is designed to improve visualisation of the bowel during colonoscopy by increasing the total surface area of the visual field. Endocuff Vision has a row of flexible patented hinged arms made from plastic, hinged at the base, which are retracted during insertion and spread out during withdrawal. These arms push out the mucosal folds of the colon allowing more of the mucosal surface to be viewed. The company claims that this can also improve the stability of the colonoscope and control of the tip. The aim of improving visualisation is to enhance the identification of colonic polyps, specifically adenomas and adenocarcinomas, and increase the likelihood of complete excision as well as helping post-excision scar examination. Before using Endocuff Vision, users will need to complete a short training session. Endocuff Vision has been selected by NHS England for the Innovation and Technology Payment (ITP) 2018/19 scheme, a programme which is supported by the Academic Health Science Networks (AHSN) and aims to remove financial and procurement barriers to uptake of innovative technologies.

Endocuff Vision received a CE mark in August 2016 as a class I medical device. Its predecessor Endocuff was CE marked in August 2011 also as a class I device.

2 Proposed use of the technology

2.1 Disease or condition

Colorectal cancer (CRC) is a cancer that starts in the colon or rectum. The majority of CRCs start out as small growths, known as polyps, on the inner lining of the colon. Over time some polyps can change and become cancerous. These polyps are called adenomas and are a pre-cancerous condition. Adenomas can lead to individuals developing CRC.

2.2 Patient group

Endocuff Vision is intended to be attached to the distal end of an endoscope for people undergoing colonoscopy:

- who have presented with unexplained change in bowel habit, iron deficiency or bleeding from the bowel (including those with positive faecal occult bloods [FOB] or faecal immunochemical test [FIT]). These are circumstances that suggest possible colorectal cancer.
- to remove known polyps, which may be difficult to find, remove or ablate because of their size, position, or previous incomplete removal.
- for surveillance, following previous adenoma removal.

CRC is the 4th most common cancer in the UK, with approximately 41,000 people being diagnosed each year (Cancer Research UK 2015). The incidence of CRC increases with age, with a sharp increase in incidence from the age of 50-54 years and the highest rates being observed in men aged 80-85 years (Cancer Research UK 2015). Patients diagnosed with CRC will be staged, typically using Dukes' classification system. Both burden of disease and risk of mortality are dependent on the stage of CRC at diagnosis, with five-year survival varying from 95% for men and 100% for women at Dukes A (Stage I) to around 5% for men and 10% for women at Dukes D (Stage IV; Cancer Research UK 2015)

2.3 Current management

NICE's guideline on suspected cancer recommends that people with suspected CRC be referred for a colonoscopy within two weeks. NICE diagnostics guidance on quantitative faecal immunochemical tests to guide referral for colorectal cancer in primary care recommends the use of 3 FITs for symptomatic patients. The FIT tests are recommended for guiding referral in people without rectal bleeding, who do not meet the criteria for a suspected cancer referral outlined in NICE's guideline on suspected cancer.

NICE's clinical guideline on colorectal cancer prevention: colonoscopic surveillance in adults with ulcerative colitis, Crohn's disease or adenomas, recommends colonoscopic surveillance for people with adenomas. The NICE guideline on colorectal cancer: diagnosis and management recommends that people with suspected CRC without major comorbidities should undergo colonoscopy to confirm their diagnosis.

The NHS Bowel Cancer Screening Programme recommends bowel cancer screening every 2 years for people age 60 to 74 years and flexible sigmoidoscopy screening for people age 55 to 60 began in England in 2013.

2.4 Proposed management with new technology

Endocuff Vision would be used as an add-on device to a standard colonoscope used for a patient undergoing colonoscopy with the aim of improving the rate of detection (and therefore removal) of polyps, notably adenomas, and allowing earlier detection of carcinomas through improved diagnostic sensitivity. There would be no change in the current care pathway.

3 Company claimed benefits and the decision problem

Details of the company's claimed benefits and the decision problem are described in Appendix D. The company submission did not propose any variations to the decision problem. The EAC noted that, although all of the evidence submitted met the final scope for the population, 3 out of 4 of the submitted studies involved people attending for screening colonoscopies. 1 of these studies also included people for surveillance after removal of polyps. Only the ADENOMA RCT involved a more heterogeneous population, and included people referred for colonoscopy for clinical symptoms.

4 The evidence

4.1 Summary of evidence of clinical benefit

The company presented 4 studies in the clinical submission. The EAC judged that all 4 were relevant to the decision problem and did not identify any further studies in its own literature review, which covered a period from 2010 to July 2018. The studies comprised 2 randomised controlled trials (RCTs): the ADENOMA trial (Ngu et al. 2018) and the E-Cap trial (Bhattacharyya et al. 2017) and 2 prospective cohort studies: Tsiamoulos et al. (2018) and Rameshshanker et al. (2016). All studies were accessed as full papers with the exception of Rameshshanker et al. (2016) which was only available as a conference abstract. The rationale for the selection of these studies is in section 3 (clinical evidence) of the assessment report. The literature searches were updated in November 2018 and 3 additional conference abstracts were identified as relevant: 1 randomised controlled trial (Geyer et al. 2018), 1 prospective pilot study (Varma et al. 2018) and 1 systematic review (Clelia et al. 2018). Only 1 study referred to Endocuff Vision (Varma et al. 2018), while the other 2 contained outcomes relevant to the question of colonoscopist expertise and the benefit of Endocuff Vision with varying baseline levels of ADR. For more information on these studies, refer to the EAC assessment report appendix.

The EAC judged that the pivotal study in the submission is the multicentre, single-blind, national ADENOMA RCT, which compared Endocuff Vision with standard colonoscopy with a 21 days follow-up (Ngu et al. 2018) in adults age 18 years and older who were referred for colonoscopy following presentation of clinical symptoms or for surveillance after removal of polyps, or who were asymptomatic but had a positive FOB test (FOBt) as part of the Bowel Cancer Screening Programme (BCSP). It found a significant increase in adenoma detection rate (ADR) for the whole population, in favour of Endocuff Vision. The other studies included in the submission also suggest that Endocuff Vision may improve ADR however they suffer from a range of methodological

limitations, which are discussed in further detail in section 3.3 of the assessment report.

The company did not perform a quantitative analysis of the evidence because it considered the RCTs differed substantially in their generalisability to real-world practice. The EAC did not conduct its own meta-analysis but referred to the meta-analysis presented by Williet et al. (2018) which included studies for Endocuff Vision and Endocuff.

EAC critical appraisal of the clinical evidence

The EAC's critical appraisal of the evidence was generally in agreement with the company's, however the following differences were noted:

- The company did not take into account performance bias due to differences in procedure
- Only one study (ADENOMA) is adequately powered to detect a difference in ADR
- The effect observed on ADR with Endocuff Vision is dependent on the colonsocopist's expertise. Using Endocuff Vision is not associated with gains in ADR for those with more expertise. As a result, the EAC considered the 3 single-centre studies (E-Cap, Rameshshanker et al. 2016 and Tsiamoulos et al. 2018) to be at risk for bias from local expertise and are not representative of UK practice as a whole. The ADENOMA RCT was the only multicentre study.
- The company consider ADR and mean adenomas per procedure to be subjective outcomes, the EAC consider them to be objective based on their definition.

For all included studies, the EAC noted a higher than average mean ADR for standard colonoscopy in a screening population (mean ADR: 50.9% to 63.0%), implying that centres had a high level of expertise in the procedure. The EAC referred to a study evaluating the quality of screening colonoscopies

in the NHS (Lee et al. 2012), which reports a mean baseline ADR of 46.5% for standard colonoscopy, with ADR ranging from 21.9% to 59.8%.

EAC clinical evidence review conclusions

Based on the limitations surrounding the rest of the evidence, the EAC concluded that the superiority of Endocuff in comparison with standard colonoscopy is supported mainly by data from the ADENOMA trial which is representative of UK practice and subject to an overall low risk of bias. In an overall colonoscopy population, the use of Endocuff Vision significantly improved ADR by 4.7% compared with standard colonoscopy and this improvement was mainly driven by significant differences in the screening population. Endocuff Vision did not lead to significant differences in ADR compared with standard colonoscopy in a non-screening population. The EAC identified operator expertise as a significant confounder that might limit the benefit of the technology in circumstances where there are already high levels of expertise and high baseline ADRs. This conclusion was supported by clinical expert advice, which stated that an increase in ADR may not be realised by endoscopists with a high baseline rate. The technology may therefore be particularly useful for clinicians with less expertise.

Table 1 Summary of key studies

Study and design	Participants / population	Intervention & comparator	Outcome measures and follow up	Results	Withdrawals	Funding	Comments
Ngu et al. (2018), prospective, single-blind, two-arm, multicentre RCT in the UK [ADENOMA]	*1,772 adult outpatients (>18 years) who were referred for clinical symptoms or as part of post-polypectomy surveillance, or were asymptomatic but tested positive to a FOBt as part of the BCSP. Patients from 7 UK centres, 57% male, mean age 62 years* *% Age <60 years* *EVC: 30.7%*	*ENDOCUFF VISION assisted colonoscopy (EVC) vs. Standard colonoscopy (SC)*	*Primary* *ADR* *Secondary* *MAP, polyp distribution, detection of SSP, rate of cuff exchange, CIT, insertion time to caecum, withdrawal time, patient experience, future colonoscopic workload due to increased ADR, difference in ADR between BCSP* and non-BCSP** colonosocopist, changes in ADR throughout the trial, colonoscopist baseline ADR*	*Mean ADR* *Overall* *EVC: 40.9%* *SC: 36.2%,* *p=0.02* *BCSP cohort* (n=797)* *EVC: 61.7%* *SC: 50.9%* *95%CI: 5.1 to∞,* *p=0.001* *Non-BCSP** (n=975)* *EVC: 24.3%* *SC:23.9%* *95%CI -4.1 to ∞* *P=0.44* *Mean MAP* *Overall:* *EVC: 0.95± 1.89* *SC: 0.75± 1.40* *P=0.20* *No significant difference in*	*All but 1 patient from the EVC group completed treatment. No patients were lost to follow-up*	*Investigator led, Industry funded adopted onto the UK NIHR portfolio.*	*Overall, good methodological quality. Only pathologist blinded. 23 adverse events of which 11 were in the EVC group were reported. No detail on the nature of these events*

Study and design	Participants / population	Intervention & comparator	Outcome measures and follow up	Results	Withdrawals	Funding	Comments
	SC:30.9% *21 days follow-up*			*MAP observed for subgroup populations*			
Bhattacharyya et al. (2017), prospective, single-blind, two-arm, single- centre RCT in the UK [E-Cap]	*531 adults (60-75 years) referred for screening or surveillance.* *64% male, mean age 68 years,* *Single centre;* *Duration of follow-up not reported*	*EVC vs SC*	*<u>Primary</u>:* *Mean number of polyps per patients (MPP)* *<u>Secondary</u>* *ADR, Advanced ADR (>10 mm in size), Adenomas per procedure, PDR, Cancer detection rate, CIT, Withdrawal times, Comfort scores,*	*<u>MPP</u>* *EVC: 70.3%* *SC: 69.8%,* *p=0.93* *<u>Mean ADR</u>* *EVC: 60.9%* *SC: 63%,* *p=0.93* *<u>Mean MAP</u>* *EVC: 1.3 ± 1.8* *SC: 1.4 ± 1.5* *(p=0.54)*	*3 patients excluded due to hyperplastic polyposis discovered during colonoscopy*	*Not reported*	*Overall, good methodological quality.* *MPP is primary outcome Currently no strong evidence to support an association between MPP and a reduction in CRC. Study only adequately powered to detect differences in MMP the evidence reported on ADR by this study cannot be considered reliable.*
Tsiamoulos et al. (2018), prospective, single-centre, non-randomised before-after	*410 adults mean age 66 (range 61-71); referred for screening colonoscopy from one UK centre*	*EVC vs SC*	*ADR, MAP, CIR, CIT, NCWT, sedation level, comfort score* *No pre-specified primary or*	*<u>Mean ADR</u>* *EVC: 68%* *SC: 52.6%* *<u>Mean MAP</u>* *EVC: 2.2* *SC: 1.2* *(P=0.007)*	*Not reported*	*Not reported*	*No sample size calculation was reported.* *This is a single-centre study. ADR rates reported from single-*

Study and design	Participants / population	Intervention & comparator	Outcome measures and follow up	Results	Withdrawals	Funding	Comments
study in the UK			*secondary outcomes*				*centre studies will be biased by the level of local expertise. Therefore, this study is at high risk for this source of bias and therefore not representative of UK practice as a whole.*
Rameshshanker et al. (2016), prospective single-centre service evaluation in UK	*96 adult patients undergoing screening colonoscopies from 1 UK centre*	*EVC vs SC*	*Assess SP6 (adenomas + sessile serrated polyps/adenomas) (primary outcome)* *ADR* *CIT* *withdrawal time* *Number of sessile serrated polyps/adenomas*	*<u>Mean ADR</u>* *EVC: 83.67%* *SC: 55.32%* *(p=0.004)* *<u>Mean MAP</u>* *EVC: 1.93* *SC: 1.08* *(p=NR)*	*Not reported*	*Not reported*	*Study reported in a conference abstract. There is insufficient information on patient characteristics and study methodology.* *This is a single-centre study. ADR rates reported from single-centre studies will be biased by the level of local expertise. Therefore, this study is at high risk for this source of bias and*

Study and design	Participants / population	Intervention & comparator	Outcome measures and follow up	Results	Withdrawals	Funding	Comments
							therefore not representative of UK practice as a whole

*Left as stated in Ngu et al. (2018). The 'BCSP' population represents asymptomatic people referred for endoscopy following a positive FOBt result as part of the BCSP.
**Left as stated in Ngu et al. (2018). The 'non-BCSP' population represents people referred for endoscopy who are either symptomatic or undergoing surveillance after polyp removal.
Abbreviations used: ADR=Adenoma detection rate; BCSP=Bowel Cancer Screening Programme; CIT=Caecal intubation rate; EVC=Endocuff Vision colonoscopy; FOBt=Faecal Occult Blood test; MAP=Mean adenoma per patient; MPP=Mean number of polyps per patient; NIHR= National Institute for Health Research; PDR=Polyp detection rate; SC=Standard colonoscopy.

4.2 Summary of economic evidence

The company submission identified 1 cost consequence study of Endocuff Vision published as a conference abstract (Conway et al. 2015). The model assumed use of Endocuff Vision increased ADR by 11.7% and results showed cost-savings of €283 per person. No quality appraisal was conducted on the study because of the limited detail available and the company considered the findings to be of limited value because it was conducted in Germany and use of data from a trial of Endocuff rather than Endocuff Vision. The EAC agreed with these decisions.

De novo analysis

The company presented an economic model comparing the costs of Endocuff Vision with standard colonoscopy in the UK for a cohort of asymptomatic people with a positive FOBt result.

The model consisted of a number of interlinked decision trees and Markov models based on a model of CRC that was used in a previous economic evaluation of CRC screening programmes (Tappenden et al. 2007; Whyte et al. 2012; Murphy et al. 2017). It captures the cost of colonoscopy, FOBt and CRC treatment according to stage at diagnosis. The structures are shown in Figure 1 and Figure 2 and full assumptions described in section 4.2 of the assessment report. Patients enter the model at age 62 and are followed for 10 years. Costs arising after the first year are discounted at a recommended rate of 3.5% per annum. The model makes some simplifying assumptions, outlined on page 53 of the assessment report.

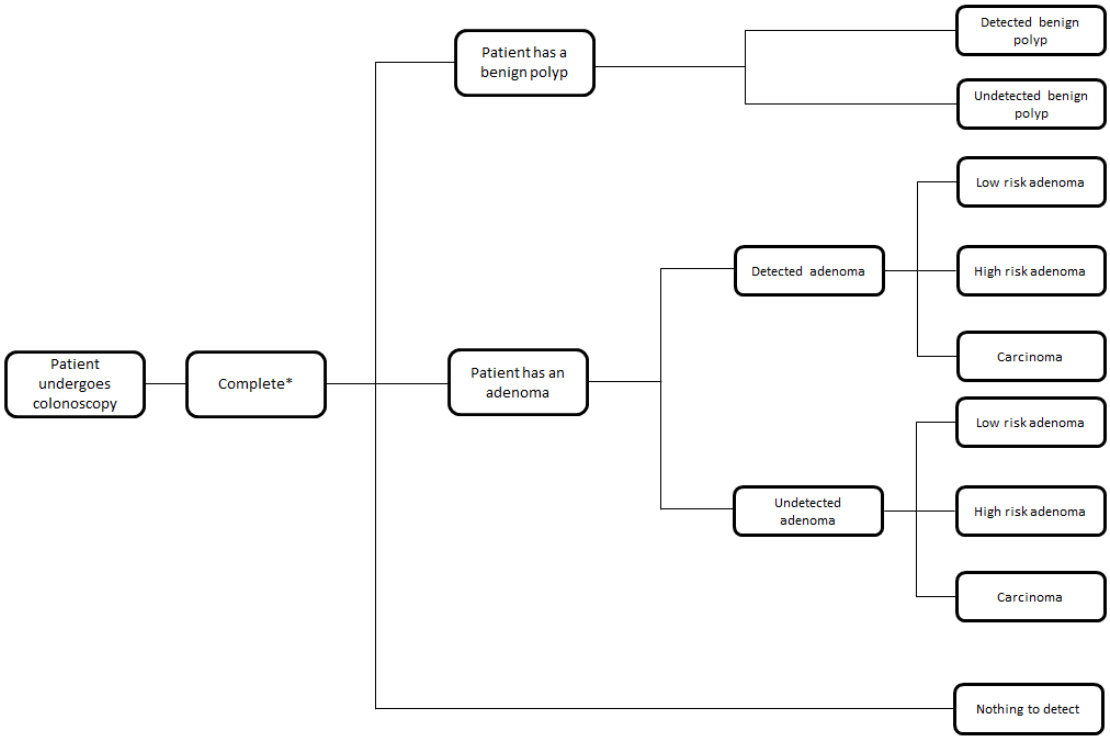

Figure 1 Decision tree to determine patient pathways following screening

*A small proportion of people have an incomplete colonoscopy. These people are assumed to undergo a second colonoscopy within the same cycle (year). The additional cost of the failed colonoscopy is captured within the model.

Figure 2 Markov model of the natural progression of CRC

Model parameters

The clinical parameters for the cost model were sourced from the available literature. Where possible the ADENOMA trial (Ngu et al. 2018) was used; other published studies were used for parameters not determined by this study. Parameters governing transitions were estimated through calibration, a standard practice in cancer modelling. Expert clinical advisers were consulted on the appropriate sources for some key parameters. The cost analysis is based on a baseline ADR with standard colonoscopy of 50.87%. A full description of the model parameters is outlined in section 4.2 page 55-56. The EAC was in agreement with the model parameters chosen.

Costs and resource use

There are two main cost parameters in the model: screening costs and CRC treatment costs. Colonoscopy costs are derived from NHS reference costs according to whether polyps were identified or not (NHS Improvement 2017), and costs of FOBt were derived from a previous evaluation of FOBt testing (Whyte et al. 2012). The company assumed the only additional cost of a

colonoscopy using Endocuff Vision would be the cost of the sleeve (£12.05). The company derived treatment costs by stage from a recent cost study carried out by Incisive Health (Incisive Health 2014).

Results from company's cost modelling

The company's de novo cost analysis estimated a saving of £12 per patient in the asymptomatic FOB-t positive cohort of patients undergoing colonoscopy over a period of 10 years. The savings arise from averted CRC and CRC diagnosed at an earlier stage through improvements in the ADR of colonoscopy with Endocuff Vision. Sensitivity analysis conducted by the company showed that cost savings are sensitive to the increase in ADR with Endocuff Vision. The company considered that an increase of 8.35% is required for Endocuff Vision to be cost neutral in the asymptomatic FOBt-positive population.

Table 2 Base case results with 10-year time horizon

	Expected cost (£)	Cost difference (£) per patient
Endocuff Vision colonoscopy	1,532	-
Standard colonoscopy	1,544	12

EAC revisions of the economic evidence

The EAC considered the basic structure of the sponsor's model to be robust. The EAC has noted two occasions where it would have selected a different parameter source to that chosen by the sponsor: the failure rate for colonoscopy and the stage distribution for screen detected and symptomatic CRC. The EAC also noted some minor errors in the execution of the sponsor's model. The EAC revised the sponsor's model in the following three ways. Firstly, it amended the errors that were noted in section 4.2 of the assessment report, primarily the application of data on the sensitivity and specificity of the FOBt test. Second, it revised the success rate for standard colonoscopy to 95.2%, matching that reported in an assessment of screening colonoscopy quality in the UK (Lee et al. 2012). The success rate for

endoscopy with Endocuff Vision was assumed to be 0.1% lower as reported in the ADENOMA trial (Ngu et al. 2018). Third, it utilised data from the UK including asymptomatic FOBt-positive patients (Sagar et al. 2015) to parameterise the stage distribution of screen-detected and symptomatic-detected CRC.The EAC revised model estimates a cost saving of £52.74 per patient in an asymptomatic FOBt-positive population over 10 years.

The EAC explored the threshold value for the ADR gain which results in Endocuff Vison being cost neutral in the model. This analysis showed that Endocuff Vision must increase ADR by at least 3.0% to offset the additional costs of its use through a reduction in CRC treatment costs. The EAC undertook two-way sensitivity analysis on the cost of CRC treatment by stage and the stage distribution of CRC in screen-detected and symptomatic patients. The EAC explored each of the sources of CRC treatment costs identified by the sponsor and combined them with German (Wiegering et al. 2016), UK (Sagar et al. 2015) and Dutch (Toes-Zoutendijk et al. 2017) stage distribution data for screen-detected and symptomatic CRC. Cost savings are larger when the English or Dutch data (in which a positive FOBt precedes screening colonoscopy) on CRC stage distributions are applied. However, the direction of cost-savings was only influenced by the source of CRC treatment costs by stage, and Endocuff Vision was cost-saving for most of the sources analysed. The results, which are presented in table 14 of the assessment report (page 65) draw the same conclusions as the original sensitivity analysis undertaken by the sponsor. The EAC concludes that cost-savings are sensitive to the differences in treatment costs for early and later stage CRC.

The EAC also undertook scenario analysis in which routine screening was undertaken using FIT rather than FOBT. In this scenario analysis the cost saving attributable to Endocuff Vision increased to £57.53 per patient in the base case.

The company's analysis considered people who were referred for endoscopy following a positive FOBt result as part of the BCSP. The EAC undertook a

subgroup analysis in which it considered the cost impact of Endocuff Vision in other patients referred for endoscopy. It applied the gain in ADR for Endocuff Vision observed in the ADENOMA trial for symptomatic patients and those referred for surveillance after polyp removal. This gain was marginal (0.4%) and the analysis indicated that Endocuff Vision is unlikely to be cost saving in this population. From the sensitivity analysis, the EAC concluded that cost increases reflect the very modest gain in ADR with Endocuff Vision in this population.

5 Ongoing research

The company identified 9 ongoing studies in the submission. The EAC ran additional searches (see section 3.9 of the assessment report) and identified a further 5 ongoing studies. Most of the studies were in the recruitment phase. One RCT comparing standard colonoscopy with Endocuff Vision was expected to complete in January 2017 but no further information was available.

6 Issues for consideration by the Committee

Clinical evidence

- The superiority of Endocuff Vision in ADR is highest in the asymptomatic FOBt-positive population. Evidence for the surveillance and symptomatic population is less robust. How generalizable are the results to these populations? Compared to an asymptomatic FOBt-positive population, symptomatic and surveillance patients are more likely to be younger and female, with lower adenoma rates (Ahmed S et al. 2016). In the UK, standards for detection have been set at a minimal ADR of 15% in a general non-screening population (Rees et al. 2016), but at 40% or more in a screening population (BCSP Standards, 2018).

- There's a positive association between colonoscopists' expertise and ADR rate. The EAC considers it is likely that use of Endocuff Vision will

not lead to an increase in ADR in centres with high expertise and in colonoscopists with high baseline ADR. What proportion of NHS centres are likely to see improvements in ADR with the use of Endocuff Vision? In what circumstances may lower baseline ADRs be observed? Due to the nature of the technology, blinding of colonoscopists was not possible in studies of Endocuff Vision. Consideration is needed around the impact of detection bias on the clinicians in the study with lower baseline ADR. What are the confounding factors that may have influenced ADR outcomes?

Cost evidence

- The EAC's cost modelling shows that use of Endocuff Vision in an asymptomatic FOBt-positive population is likely to be cost saving. How generalizable are these results to other patients referred for endoscopy, such as people presenting with clinical symptoms or those undergoing surveillance after polyp removal? Using evidence from the ADENOMA trial, Endocuff Vision is unlikely to save costs in these patients.

- The EAC's sensitivity analysis shows an improvement in ADR above 3.0% is sufficient to generate cost savings through reduced CRC treatment costs. Data from ADENOMA indicates that this size improvement is likely with Endocuff Vision in an asymptomatic FOBt-positive population. Is it achievable across the NHS in real-world practice?

7 Authors

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NICE Medical Technologies Evaluation Programme

November 2018

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

Details of assessment report:

- Chalkidou A, Erskine J, Keevil S, Lanford T, Macmillan T, Pennington M. Endocuff Vision for endoscopic investigation (August 2018)

Submissions from the following sponsors:

- Norgine

Related NICE guidance

- NICE guideline on suspected cancer: recognition and referral
- NICE guideline on colorectal cancer prevention

References

Ahmed S, Naumann DN, Karandikar S (2016) Differences in screening vs non-screening colonoscopy: scope for improvement? Colorectal Disorders 18(9), 903–9

Gov.UK (2018). Bowel Cancer Screening Programme (BCSP) standards [online; accessed 23 November 2018]

Rees CJ, Gibson ST, Rutter MD et al. (2016) UK key performance indicators and quality assurance standards for colonoscopy. Gut 65(12), 1923–9

Please see EAC assessment report starting on page 70 for a full list of all other references.

Appendix B: Comments from professional bodies

Expert advice was sought from 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.

Dr Anjan Dhar
Reader in medicine, Consultant Gastroenterologist, Clinical Lead for Gastroenterology and UGI Cancers, County Durham & Darlington NHS Foundation Trust. A member of the Data Monitoring Committee for the ADENOMA RCT.

Mr Neil Philip James Cripps
Consultant Colorectal Surgeon and Chair, Colonoscopy Sub-Committee ACPGBI. No conflict of interest declared.

Dr Noriko Suzuki
Consultant Endoscopist, St Marks' Hospital. No conflict of interest declared.

- The experts thought that ADR is the best metric to predict reduction in interval cancers and that there is generally an inverse relationship between ADR and risk of colorectal cancer.
- The experts thought that an increase in ADR would likely only be observed in colonoscopists with less expertise.

Appendix C: Comments from patient organisations

Advice and information was sought from patient and carer organisations during the scoping phase. The following patient organisations were contacted and no response was received:

- Beating Bowel Cancer
- Action Cancer - NI
- Bladder and Bowel UK
- BME cancer communities
- Bowel Cancer Information (Formerly Lynn's Bowel Cancer Campaign)
- Bowel Cancer UK
- Cancer Black Care
- Cancer Equality
- CancerHelp UK
- Helen Rollason Cancer Charity
- Independent Cancer Patients' Voice
- Macmillan Cancer Support
- Tenovus Cancer Care
- Ulster Cancer Foundation

Appendix D: Decision problem and claimed benefits

The benefits to patients claimed by the company through the use of Endocuff Vision in colonoscopy are:

- Significantly increased diagnostic yield: more cancerous and pre-cancerous polyps can be identified, potentially enabling earlier detection of cancer.
- More polyps are fully excised, which may reduce the need to refer patients to more specialist services for expert clinical care or open surgery, which may entail more travelling for the patient.
- Better evaluation of post-excision scars, which may reduce unnecessary repeat procedures and avoid tumour recurrence.
- Greater operator confidence in the colonoscopic procedure: patients may be given more accurate post-procedural information based on higher procedure sensitivity, allowing the correct post-procedural surveillance protocol to be followed and potentially reducing the risk of subsequent cancers or unnecessary procedures.
- Easier access to electrocoagulation for angiodysplasia, potentially reducing the number of repeat colonoscopies.

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

- Fewer missed cancers, which may be associated with the treatment of earlier cancers rather than advanced ones, resulting in fewer appointments, less chemotherapy, less radiotherapy, fewer additional tests, reduced in-patient time, less palliative treatment and less litigation.
- Through better removal of pre-malignant lesions, fewer cancers in the future with substantial savings in staff, consumables, surgery, and other treatments that would have been needed.
- More effective adenoma removals, polyp excisions and electrocoagulation, potentially leading to fewer recurrences or less need for open surgery, follow-ups, tests and treatment as listed above.

	Scope issued by NICE
Population	People undergoing colonoscopy for suspected bowel cancer, for the removal of known polyps and for surveillance because of a higher than average risk of colorectal cancer in line with NICE guideline on colorectal cancer prevention.
Intervention	Colonoscopy with the addition of an Endocuff Vision device
Comparator(s)	Colonoscopy
Outcomes	The outcome measures to consider include: Procedural outcomes: • MAP, mean number of adenomas detected per procedure • ADR overall and ADR by location in the colon (right or left) • type of polyp (e.g. sessile serrated polyp) • size of polyp (diminutive, small and large) • overall procedure time (time to caecal intubation, time to withdrawal) • caecal intubation rates • number of repeat colonoscopies and sub-optimal examinations • polyp distribution in different parts of the colon Cancer diagnosis and management • incidence of subsequent interval cancers • rate of diagnosis of bowel cancer • referral rates for specialist treatment and rates of subsequent surgery, chemotherapy and radiotherapy • tumour recurrence after colonoscopic resection • rate of repeat colonoscopy after electrocoagulation for angiodysplasia Patient outcomes • patient comfort and experience • device-related adverse events for example complication rate (mucosal lacerations or major bleeding, perforation or loss of Endocuff Vision)
Cost analysis	Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be sufficiently long to reflect any 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	• People referred for colonoscopy through the NHS bowel cancer screening programme • People offered colonoscopic surveillance because they have had adenomas removed • People offered colonoscopy after reporting symptoms

Special considerations, including those related to equality	Endocuff Vision cannot be used for small bowel investigations	
	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?	Yes
	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
	People with colonic strictures, acute diverticulitis and acute colitis cannot have colonoscopies and so cannot use Endocuff Vision; these people may be considered disabled if their condition has a substantial and long term adverse effect on their ability to carry out normal day to day activities for more than 12 months	

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology guidance

SCOPE

Endocuff Vision for endoscopic investigation

1 Technology

1.1 Description of the technology

Endocuff Vision is a single-use disposable device which fits over the end of most conventional colonoscopes and is designed to improve visualisation of the bowel during colonoscopy by increasing the total surface area of the visual field. Endocuff Vision has a row of flexible arms, hinged at the base, which are retracted during insertion and spread out during withdrawal. These arms push out the mucosal folds of the colon allowing more of the mucosal surface to be viewed. The company claims that this can also improve the stability of the colonoscope and control of the tip. The aim of improving visualisation is to enhance the identification of colonic polyps, specifically adenomas and adenocarcinomas, and increase the likelihood of complete excision as well as helping post-excision scar examination. Prior to using Endocuff Vision, users will need to complete a short training session. Endocuff Vision has been selected by NHS England for the Innovation and Technology Payment (ITP) 2018/19 scheme.

1.2 Regulatory status

The first Endocuff device was CE marked in August 2011 as a Class I sterile medical device and this was renewed for the successor product, Endocuff Vision, in August 2016. Endocuff Vision differs from Endocuff in having one row of longer (15 mm vs. 12 mm) arms instead of two shorter ones.

1.3 Claimed benefits

The benefits to patients claimed by the company through the use of Endocuff Vision in colonoscopy are:

- Significantly increased diagnostic yield: more cancerous and pre-cancerous polyps can be identified, potentially enabling earlier detection of cancer.
- More polyps are fully excised, which may reduce the need to refer patients to more specialist services for expert clinical care or open surgery, which may entail more travelling for the patient.
- Better evaluation of post-excision scars, which may reduce unnecessary repeat procedures and avoid tumour recurrence.
- Greater operator confidence in the colonoscopic procedure: patients may be given more accurate post-procedural information based on higher procedure sensitivity, allowing the correct post-procedural surveillance protocol to be followed and potentially reducing the risk of subsequent cancers or unnecessary procedures.
- Easier access to electrocoagulation for angiodysplasia, potentially reducing the number of repeat colonoscopies.

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

- Fewer missed cancers, which may be associated with the treatment of earlier cancers rather than advanced ones, resulting in fewer appointments, less chemotherapy, less radiotherapy, fewer additional tests, reduced in-patient time, less palliative treatment and less litigation.
- Through better removal of pre-malignant lesions, fewer cancers in the future with substantial savings in staff, consumables, surgery, and other treatments that would have been needed.
- More effective adenoma removals, polyp excisions and electrocoagulation, potentially leading to fewer recurrences or less need for open surgery, follow-ups, tests and treatment as listed above.

1.4 Relevant diseases and conditions

Endocuff Vision is intended for use in people undergoing colonoscopy:

- who have presented with unexplained change in bowel habit, iron deficiency or bleeding from the bowel (including those with positive faecal occult bloods (FOB) or faecal immunochemical test (FIT)). These are circumstances that suggest possible colorectal cancer
- to remove known polyps, which may be difficult to find, remove or ablate because of their size, position, or previous incomplete removal.

- for surveillance, following previous adenoma removal.

Colorectal (lower bowel) cancer is the fourth most common cancer, and the second most common cause of cancer death in the UK. Two-thirds of colorectal cancers develop in the colon – the remaining third develop in the rectum.

Colonoscopy is the standard procedure for the identification of colorectal cancer and pre-cancer. In 2015 41,804 new colorectal cancers were diagnosed (Cancer Research UK). Some cancers and precancerous polyps are missed at diagnostic colonoscopy; the likelihood of this happening is estimated to be between 6% and 8%, equating to between 1,896 - 2,528 missed cancers in England every year. Miss-rates are particularly high for small adenomas (less than 5 millimetres), for which the miss-rate has been estimated to be as high as 27%.

If a cancer is diagnosed within 6 months to 3 years (or 5 years, depending on the study design) of a negative diagnostic colonoscopy, it is referred to as an interval cancer. One study reported that 2.9% of all colorectal cancers diagnosed were interval cancers, and suggested that the majority of these (86%) could have been prevented. Studies conducted in the USA have found that around 6 to 7% of people undergoing colonoscopy subsequently developed interval cancers and that in some cases, these could be classed as missed by previous colonoscopy. There are clinical risk factors for the development of an interval cancer, such as proximal tumour location, increased co-morbidities, or a pre-existing diagnosis of diverticulitis. Procedural risk includes the procedure being undertaken by an endoscopist with a low adenoma detection rate (ADR), or by a non-specialist (not a

gastroenterologist). Under these circumstances, the relevant factors may relate to lack of experience or expertise.

1.5 Current management

The current NHS care pathway for a person undergoing colonoscopic investigation is described by several guidelines.

Bowel Cancer Screening Programme

The UK National Screening Committee recommendations on bowel cancer screening are currently under review and are expected to be completed by August 2018. Currently the NHS uses one of two methods to screen for bowel cancer:

- bowel scope screening (flexible sigmoidoscopy) is provided as a one-off bowel scope screening for people aged 55 years of age or older and is currently only available to people in England.

- faecal occult blood (FOB) home testing kits are automatically sent to all people aged 60 to 74 years who are registered with a GP. They can use the test at home and then post to a laboratory for testing. FOB tests will be sent to people in this age group every two years until they reach the maximum screening age.

People over 60 years with abnormal FOB test screening results will be offered a colonoscopy to check for polyps further up the bowel if repeat FOB tests are also abnormal. People with abnormal bowel scope screening results may also be offered a colonoscopy. People younger than 55 or older than 74 years may also receive screening but it is not routine practice to do so.

Symptomatic presentation

NICE guideline on suspected cancer: recognition and referral (lower gastrointestinal tract cancers) recommends that in general, a person presenting with symptoms suggestive of colorectal or anal cancer should be seen by a specialist service within 2 weeks. The guideline describes in detail

symptoms which should trigger a referral, especially in patients aged 40 years or older with unexplained weight loss, abdominal pain, rectal bleeding, iron-deficiency anaemia, changes in bowel habit or a lower abdominal or rectal mass.

NICE guideline on colorectal cancer: diagnosis and management: recommends that people with suspected colorectal cancer whose condition is being managed in secondary care should be advised that more than one investigation may be needed to confirm or exclude diagnosis. Colonoscopy should be offered to patients who do not have any major comorbidity to confirm diagnosis of colorectal cancer. If a lesion suspicious of cancer is detected a biopsy should be undertaken to obtain histological proof of diagnosis unless it is contraindicated. Other methods of diagnosis such as flexible sigmoidoscopy or computed tomographic colonography may be used.

NICE guideline on colorectal cancer prevention states that people with inflammatory bowel disease whose symptoms started over 10 years ago and who have ulcerative colitis (UC) (but not proctitis alone), people with Crohn's colitis involving more than one segment of colon and people with adenomas should be offered colonoscopic surveillance. The frequency of colonoscopic surveillance should be once every 1 to 5 years depending on the patient's risk of developing colorectal cancer.

The introduction of Endocuff Vision would leave the current patient pathway of care up to the time of colonoscopy unaltered. Endocuff Vision is designed to increase the diagnostic sensitivity of all colonoscopies, resulting in fewer false negatives and increasing the ADR and mean number of adenomas detected per procedure (MAP). By fully removing cancerous and pre-cancerous polyps at an earlier stage of the pathway, there is the potential to avoid the need for patients to undergo treatment for a more advanced cancer at a later stage. The British Society of Gastroenterology quality standards for colonoscopy aim for a minimal ADR of 15% for the UK all age population.

NICE diagnostic guidance recommends that in some circumstances virtual chromoendoscopy be used to assess polyps of 5 mm or less during

colonoscopy, instead of histopathology, to determine if the polyps are adenomatous or hyperplasia. NICE has also recommended that quantitative faecal immunochemical tests be used to guide referral for colorectal cancer in primary care.

2 Statement of the decision problem

	Scope issued by NICE
Population	People undergoing colonoscopy for suspected bowel cancer, for the removal of known polyps and for surveillance because of a higher than average risk of colorectal cancer in line with NICE guideline on colorectal cancer prevention.
Intervention	Colonoscopy with the addition of an Endocuff Vision device
Comparator(s)	Colonoscopy
Outcomes	The outcome measures to consider include: Procedural outcomes: •MAP, mean number of adenomas detected per procedure •ADR overall and ADR by location in the colon (right or left) •type of polyp (e.g. sessile serrated polyp) •size of polyp (diminutive, small and large) •overall procedure time (time to caecal intubation, time to withdrawal) •caecal intubation rates •number of repeat colonoscopies and sub-optimal examinations •polyp distribution in different parts of the colon Cancer diagnosis and management •incidence of subsequent interval cancers •rate of diagnosis of bowel cancer •referral rates for specialist treatment and rates of subsequent surgery, chemotherapy and radiotherapy •tumour recurrence after colonoscopic resection •rate of repeat colonoscopy after electrocoagulation for angiodysplasia Patient outcomes •patient comfort and experience •device-related adverse events for example complication rate (mucosal lacerations or major bleeding, perforation or loss of Endocuff Vision)
Cost analysis	Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be sufficiently long to reflect any 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	• People referred for colonoscopy through the NHS bowel cancer screening programme

	• People offered colonoscopic surveillance because they have had adenomas removed • People offered colonoscopy after reporting symptoms	
Special considerations, including those related to equality	Endocuff Vision cannot be used for small bowel investigations	
	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?	Yes
	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
	People with colonic strictures, acute diverticulitis and acute colitis cannot have colonoscopies and so cannot use Endocuff Vision; these people may be considered disabled if their condition has a substantial and long term adverse effect on their ability to carry out normal day to day activities for more than 12 months	

NICE may undertake, as part of this evaluation, additional technical assessment of issues including device compatibility.

3 Related NICE guidance

Published

Clinical guidelines

- Suspected cancer: recognition and referral (2015)
- Colorectal cancer: diagnosis and management (2011)
- Colorectal cancer prevention: colonoscopic surveillance in adults with ulcerative colitis, Crohn's disease or adenomas (2011)
- Improving outcomes in colorectal cancer (2004)

Technology appraisal guidance

- Trifluridine–tipiracil for previously treated metastatic colorectal cancer (2016)

- Aflibercept in combination with irinotecan and fluorouracil-based therapy for treating metastatic colorectal cancer that has progressed following prior oxaliplatin-based chemotherapy (2014)
- Cetuximab, bevacizumab and panitumumab for the treatment of metastatic colorectal cancer after first-line chemotherapy (2012)
- Bevacizumab in combination with oxaliplatin and either fluorouracil plus folinic acid or capecitabine for the treatment of metastatic colorectal cancer (2010)
- Cetuximab for the first-line treatment of metastatic colorectal cancer (2009)
- Bevacizumab and cetuximab for the treatment of metastatic colorectal cancer (2007)
- Laparoscopic surgery for colorectal cancer (2006)
- Capecitabine and oxaliplatin in the adjuvant treatment of stage III (Dukes' C) colon cancer (2006)
- Guidance on the use of capecitabine and tegafur with uracil for metastatic colorectal cancer (2003)

Interventional procedures guidance

- Low energy contact X-ray brachytherapy (the Papillon technique) for early stage rectal cancer(2015)
- Preoperative high dose rate brachytherapy for rectal cancer (2015)
- Transanal total mesorectal excision of the rectum (2015)
- Combined endoscopic and laparoscopic removal of colonic polyps (2014)
- Endoscopic submucosal dissection of lower gastrointestinal lesions (2010)
- Selective internal radiation therapy for non-resectable colorectal metastases in the liver (2011)
- Radiofrequency ablation for colorectal liver metastases (2009)
- Computed tomographic colonography (virtual colonoscopy) (2005)
- Complete cytoreduction for pseudomyxoma peritonei (Sugarbaker technique) (2004)

Diagnostic guidance

- Molecular testing strategies for Lynch syndrome in people with colorectal cancer (2017)
- Quantitative faecal immunochemical tests to assess symptomatic people who are at low risk of colorectal cancer in primary care (2017)
- Virtual chromoendoscopy to assess colorectal polyps during colonoscopy (2017)

Under development

NICE is developing the following guidance (details available from www.nice.org.uk):

Clinical guidelines

- Colorectal cancer: diagnosis and management (update). Expected publication date October 2019

Technology appraisal guidance

- Atezolizumab for treating metastatic colorectal cancer after 2 therapies Expected publication date TBC
- Nivolumab with ipilimumab for treating metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency. Expected publication date TBC

4 External organisations

4.1 Professional organisations

4.1.1 Professional organisations contacted for expert advice

At the selection stage, the following societies were contacted for expert clinical and technical advice:

- Association of Coloproctology of Great Britain and Ireland (ACPGBI)
- British Society of Gastroenterology
- Royal College of Surgeons

4.1.2 Professional organisations invited to comment on the draft scope

The following societies have been alerted to the availability of the draft scope for comment:

- Association of Coloproctology of Great Britain and Ireland
- British Society of Gastroenterology
- Royal College of Surgeons
- Royal College of Physicians
- British Society of Paediatric Gastroenterology, Hepatology and Nutrition.

4.2 Patient organisations

At the selection stage, NICE's Public Involvement Programme contacted the following organisations for patient commentary and alerted them to the availability of the draft scope for comment:

- Beating Bowel Cancer
- Bowel Cancer Information (Formerly Lynn's Bowel Cancer Campaign)
- Bowel Cancer UK
- Cancer Research UK
- Cancer Support UK
- CORE (Digestive Disorders Foundation)
- Helen Rollason Cancer Charity
- Help Adolescents With Cancer (HAWC)
- Independent Cancer Patients' Voice
- Macmillan Cancer Support
- Pelican Cancer Foundations
- Pelvic Pain Support Network
- Penny Brohn Cancer Care
- Tenovus

Medicines and Technologies Programme
Adoption Scoping Report MT250 Endocuff Vision

SUMMARY

Adoption Levers

- No need to increase sedation levels to establish tolerance.
- Good patient tolerance and safety with accurate size selection.
- Identified for one of NHSE's Innovative Technology Payments (ITP) 2018/19 and available to order using zero cost model (no upfront costs to purchaser).

Adoption Barriers

- Clinical need not routinely accepted. Senior clinicians with high adenoma detection rate (ADR) may believe it is not necessary.
- Patient selection is important to help prevent procedure failure and associated poor confidence in the technology.
- Med Tech Guidance due for publication May 2019 and ITP only guaranteed until April 2019. Potential extension arrangements not yet available.

1. Introduction

The adoption team has collated information from:

- Healthcare professionals working within NHS organisations (all of whom have experience of using Endocuff Vision) - 3 consultant gastroenterologists working with adults, one of whom is an adjunct professor of endoscopy.
- NHS England with regard to Innovation Technology Payment (ITP) arrangements.
- Norgine – the manufacturer.

An additional 12 clinicians were contacted but they either failed to respond or declined to engage.

This adoption scoping report (ASR) includes some of the benefits and difficulties that may be faced by organisations when planning to adopt the technology into routine NHS use. It is the first ASR to be prepared on a technology that has been awarded an NHSE ITP.

2. Use of Endocuff Vision in practice

The manufacturer advised that as of April 2018, 10 NHS hospitals were routinely ordering Endocuff Vision.

The 3 contributors have varying experience of Endocuff:

- 1 uses routinely for both bowel screening and symptomatic patients.
- 1 used as part of a RCT but rarely uses now.
- 1 trialled a free sample of 12 but did not continue due to perceived lack of benefit and cost at the time.

All 3 acknowledged the indication for use in bowel screening patients (and 2 mentioned patients who come in on a surveillance list with previous polyps). None were using in the small bowel and were aware of the contraindications.

No contributors were aware of the NHSE ITP status or the existence of the ITP but expected use of Endocuff Vision to increase because of this.

3. Reported benefits

The benefits of adopting Endocuff Vision as reported to the adoption team by the healthcare professionals using the technology are:

- Improved ADR for endoscopists, particularly junior level.
- Useful in bowel screening population.
- Helps to stabilise the tip of the scope making polyp excision easier.
- Improves visualisation and thus confidence that the whole colon has been explored.

4. Levers and barriers to adoption

The key considerations for adoption highlighted through discussions with contributors are:

Commissioning and Procurement

The NHS ITP programme aims to support the NHS in adopting innovation by removing financial or procurement barriers to uptake of innovative products or technologies.

An innovation specification is available within the Technical Notes on the NHSE website. From April 2018, Endocuff Vision can be ordered by email from Norgine Pharmaceuticals Ltd under the zero cost model. There is a minimum order of three boxes.

The innovation specification states the following acceptance and exclusion criteria:

NHS sites adopting this technology must

- only use Endocuff Vision attachments with compatible colonoscopes
- ensure staff are trained in the correct use of Endocuff Vision
- follow instructions for use and use correct Endocuff Vision size in accordance with the scope being used
- not use the technology for complex sub-mucosal dissection where a separate distal attachment is required.

Sites should be aware that Endocuff Vision**:**

- is not intended for deep ileal intubation
- should not be used in cases with acute, severe colitis or where there is known colonic stricture.

The current incentive is limited to April 2019 to enable NHSE to evaluate evidence of benefits. Arrangements beyond this date are as yet unclear.

Outside this arrangement, Endocuff Vision can be ordered via NHS Supply Chain.

Patient Selection

All contributors agreed that people with positive faecal occult blood tests following bowel screening would be the intended population to consider for colonoscopy with Endocuff Vision. Two contributors also mentioned using the device in people with known polyps (for surveillance).

Outside of bowel screening and polyp surveillance, all contributors stated they would not use Endocuff Vision. Each of the contributors were aware that it is not suitable for small bowel intubation nor in colonoscopies for IBD or strictures.

As the device is plastic, ridged and slightly increases the diameter of the scope, one contributor explained that use in very tense patients and those who refuse sedation would lead to a high procedure failure rate and that training should mitigate this potential barrier.

Clinician confidence / acceptance

Two contributors stated that experienced endoscopists with existing high ADRs, may feel the device is not necessary, but stated it could have higher appeal and be useful for more junior colleagues.

One contributor disagreed and said that constant striving for improvement should be everyone's concern. This contributor also reported improvement in successful polyp excisions as well as ADR.

One contributor stated that ADR is influenced by a number of factors such as time pressure, list size, fatigue and getting sedation right (to achieve patient comfort and tolerance) and having Endocuff Vision won't alter these.

NHSE expected outcome (as stated in technical notes) is a relative increase in the ADR of up to 21% plus increased likelihood of complete excision.

Training

The manufacturers have instructions and demonstration videos available on their website.

Selecting the correct size for the scope is important to ensure it does not come off (see Safety, below). Contributors reported it is easy to select the correct size cuff according to the size of colonoscope used. The manufacturer has a compatibility schedule on the product website making it easy to see which size to order to suit local equipment. This should be included in the training.

Contributors held different views on training requirements (largely dependent upon their own level of endoscopy experience):

- 1 reported that at least 20 supervised cases (ideally 30) were needed. This contributor was evaluating under rigorous clinical trial conditions.

- 1 had no training or supervised cases and considered a demonstration and brochure to be sufficient.

- 1 stated it was easy to use and required no special training for set up and application, but that training should be focused around patient selection, using the correct size cuff and knowing when to pull back and withdraw.

Governance

ITP technologies are subject to monitoring through data collection. NHSE is working with Norgine to develop a device registry. For more information contact the NHS England Innovation and Research Unit at england.innovation@nhs.net.

The outcome of this registry data may affect ongoing funding arrangements which is likely to influence ongoing use and/or longer term adoption.

Data collection was not considered to be a barrier to adoption as ADR is included in the British Society of Gastroenterology UK Key Performance Indicators & Quality Assurance Standards for Colonoscopy. All colonoscopists are expected to monitor their ADR detection rate and achieve a minimal 15% and aspirational 20%. Measuring ADR currently requires interrogation of pathology databases to obtain polyp histology.

Patient experience and safety

One contributor stated that whilst using a free trial sample of 12 devices it was well tolerated. He also reported good safety with no incidences of the Endocuff coming off/falling off.

One contributor had one episode of it coming off in a total of 2-3,000 uses. He puts this down to not selecting the correct size early on in its adoption (see Training above).

This contributor also cited the importance of correct patient selection and knowing when to pull back as a key factor in ensuring safe use and avoid complications such as scratching or perforation

5. Comparators

EndoRings: The EndoRings Distal Attachment is an endoscopic add-on device made from silicon. It has a short tube-like core with several layers of flexible circular rings. EndoRings is designed to fit a variety of endoscopes.

Transparent caps: Transparent caps were first designed to aid visualisation during endoscopic mucosal resection procedures to remove cancerous or other lesions, and are used also used for diagnostic purposes. There are a wide variety of transparent endoscopic caps available.

None of the contributors had experience with either of these.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical Technologies Evaluation Programme

Sponsor submission of evidence:

Evaluation title: Endocuff Vision for Endoscopic Investigation

Sponsor: Norgine

Date sections A and B submitted: 22 June 2018

Date section C submitted: 20 July 2018

August 2011 (Version 1.1)

Contents

Instructions for Sponsors

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the Medical Technologies Evaluation Programme process for developing NICE medical technologies guidance. Use of the submission template is mandatory.

The purpose of the submission is for the sponsor to collate, analyse and present all relevant evidence that supports the case for adoption of the technology into the NHS in England, within the scope defined by NICE. Failure to comply with the submission template and instructions could mean that the NICE cannot issue recommendations on use of the technology.

The submission should be completed after reading the 'Medical Technologies Evaluation Programme Methods guide' and the 'Medical Technologies Evaluation Programme Process guide' available at www.nice.org.uk/mt. After submission to, and acceptance by, NICE, the submission will be critically appraised by an External Assessment Centre appointed by NICE.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence'). When data are 'commercial in confidence' or 'academic in confidence', it is the sponsor's responsibility to highlight such data clearly. For further information on disclosure of information, submitting cost models and equality issues, users should see Section 11 of this document 'Related procedures for evidence submission'.

The submission should be concise and informative. The main body of the submission should not exceed 100 pages (excluding the pages covered by the template and appendices). The submission should be sent to NICE electronically in Word or a compatible format, not as a PDF file.

The submission must be a stand-alone document. Additional appendices may only be used for supplementary explanatory information that exceeds the level

of detail requested, but that is considered to be relevant to the case for adoption. Appendices will not normally be presented to the Medical Technologies Advisory Committee when developing its recommendations. Any additional appendices should be clearly referenced in the body of the submission. Appendices should not be used for core information that has been requested in the specification. For example, it is not acceptable to attach a key study as an appendix and to complete the economic evidence section with 'see Appendix X'.

All studies and data included in the submission must be referenced. Identify studies by the first author or trial ID, rather than by relying on numerical referencing alone, (for example, 'Trial 123/Jones et al.[126], rather than 'one trial[126]'). Please use a recognised referencing style, such as Harvard or Vancouver.

The sponsor should provide a PDF copy of full journal articles or reports – in electronic or hard copy form – included in the submission, if the sponsor is either the copyright owner or has adequate copyright clearance to permit the intended use by NICE. This clearance must be wide enough to allow NICE to make further copies, store the article electronically for a limited period of time on a shared drive to be accessed by a limited number of staff. Additionally, any full article obtained and submitted in electronic format must be done so in a manner compliant with the relevant contractual terms of use permitting the sponsor electronic access to the article. If the sponsor does not have sufficient copyright clearance, they are asked to submit references or links only, or details of contacts for unpublished research. NICE will then itself obtain full copies of all relevant papers or reports, paying a copyright fee where necessary. For unpublished studies for which a manuscript is not available, provide a structured abstract about future journal publication. If a structured abstract is not available, the sponsor must provide a statement from the authors to verify the data provided.

If a submission is based on preliminary regulatory recommendations, the sponsor must advise NICE immediately of any variation between the preliminary and final approval.

Document key

Boxed text with a grey background provides specific and/or important guidance for that section. This should not be removed.

Information in highlighted black italic is to help the user complete the submission and may be deleted.

The user should enter text at the point marked ‘Response’ or in the tables as appropriate. ‘Response’ text may be deleted.

List of Tables

List of Figures

Abbreviations

Term	Definition
ACG	America College of Gastroenterology
ACPGBI	Association of Coloproctology for Great Britain and Ireland
ADR	Adenoma detection rate
AMR	Adenoma miss rates
BCSP	Bowel Cancer Screening Programme
BMJ	British Medical Journal
BSG	British Society of Gastroenterology
CASP	Critical Appraisal Skills Programme
CDSR	Cochrane Database of Systematic Reviews
CE	Cost effectiveness
CEA	Cost Effectiveness Analysis Registry
CI	Confidence intervals
CIR	Caecal intubation rates
CIT	Caecal intubation time
CPCI	Conference proceedings citation index
CRC	Colorectal cancer
CRD	Centre for Reviews and Dissemination
CT	Computerised Tomography
DARE	Database of Abstracts of Reviews of Effects
DDW	Digestive Disease Week
ECV	Endocuff Vision
EEPRU	Policy Research Unit in Economic Evaluation of Health and Care Interventions
EMR	Endoscopic mucosal resection
FDA	Food and Drug Administration
FOBT	Faecal occult blood test
HRG	Healthcare resource groups
HTA	Health Technology Assessment
ICTRP	International Clinical Trials Registry Portal
IQR	Interquartile Range
ITT	Intention to treat
KOL	Key Opinion Leader
MAP	Mean number of adenomas per patient
MAUDE	Manufacturer and User Facility Device
MHRA	Medicines and Healthcare products Regulatory Agency
MPP	Mean number of polyps per patient
MTEP	Medical Technologies Evaluation Programme
NA	Not applicable
NCWT	Negative colonoscopy withdrawal time
NHMRC	National Health and Medical Research Council
NHS	National Health Service
NHSEED	National Health Service Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
NR	Not reported
OPCS	Office of population, censuses and surveys classification
PbR	Payment by results
PDR	Polyp detection rate
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Term	Definition
PRO	Patient reported outcomes
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
RCT	Randomised controlled trials
SC	Standard care
SD	Standard Deviation
SE	Standard Error
SR	Systematic review
SSP	Sessile serrated polyps
UEG	United European Gastroenterology
UK	United Kingdom
US	United States
WHO	World Health Organisation

Section A – Decision Problem

Section A describes the decision problem, the technology and its clinical context. There is also information about ongoing studies, regulatory information and equality issues.

Sponsors should submit section A before the full submission (for details on timelines, see the NICE document 'Guide to the Medical Technologies Evaluation Programme process', available from www.nice.org.uk/mt

1 Statement of the Decision Problem

The decision problem is specified in the final scope issued by NICE. The decision problem states the key parameters that should be addressed by the information in the evidence submission. All statements should be evidence based and directly relevant to the decision problem.

Table A1: Statement of the decision problem

	Scope issued by NICE	Variation from scope	Rationale for variation
Population	People undergoing colonoscopy for suspected bowel cancer, for the removal of known polyps and for surveillance following previous adenoma removal.	None.	
Intervention	Colonoscopy with the addition of an Endocuff Vision® device	None.	
Comparator(s)	Colonoscopy	None.	
Outcomes	The outcome measures to consider include: • Procedural outcomes • Mean number of adenomas detected per procedure (MAP) • Adenoma detection rate (ADR) overall and ADR by location in the colon (right or left) • Type of polyp (e.g. Sessile serrated polyp) • Size of polyp (diminutive, small and large) • Overall procedure time (time to caecal intubation, time to withdrawal, training time on using Endocuff Vision®) • Caecal intubation rates • Number of repeat colonoscopies and sub-optimal examinations • Polyp distribution in different parts of the colon Cancer diagnosis and management: • Rate of diagnosis of bowel cancer • Referral rates for specialist treatment and rates of subsequent surgery, chemotherapy and radiotherapy • Tumour recurrence after colonoscopic resection • Rate of repeat colonoscopy after electrocoagulation for angiodysplasia Patient outcomes: • Patient comfort and experience • Device-related adverse events for example complication rate (mucosal lacerations or major bleeding, perforation or loss of Endocuff Vision®)	None. However, there was no evidence identified for the following outcomes in the scope: • Referral rates for specialist treatment and rates of subsequent surgery, chemotherapy and radiotherapy • Tumour recurrence after colonoscopy resection • Rate of repeat colonoscopy after electrocoagulation for angiodysplasia • Incidence of subsequent interval cancers	

	Scope issued by NICE	Variation from scope	Rationale for variation
Cost analysis	Comparator(s): Standard colonoscopy Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be sufficiently long to reflect any 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.	None.	
Subgroups to be considered	People referred for colonoscopy through the NHS bowel cancer screening programme. People offered colonoscopic surveillance because they have had adenomas removed. People offered colonoscopy after reporting symptoms to a general practitioner.	No variation in clinical review. People offered colonoscopy after reporting symptoms to a general practitioner were not considered in the cost analysis due to statistically significant benefit of using ENDOCUFF VISION® not yet being demonstrated in this group.	
Special considerations, including issues related to equality	Endocuff Vision® cannot be used for small bowel investigations.	None.	

If the sponsor considers that additional parameters should be included in the submission, which are not stated in the decision problem, this variation from the scope and the rationale for it must be clearly described in the relevant columns in Table A1.

2 Description of Technology Under Assessment

2.1 Give the brand name, approved name and details of any different versions of the same device.

The brand name of the device is ENDOCUFF VISION®. It is a single-use, disposable Class 1 sterile medical device that fits securely around the tip of a compatible colonoscope. It is made of a soft plastic material and contains a single set of flexible hinged arms that once attached to the colonoscope form a ring around the head. An earlier version of the device, ENDOCUFF™, also exists. Three adaptations to the ENDOCUFF™ were made when updating to ENDOCUFF VISION®:

- A single row of arms, rather than two rows of arms;
- Longer circumferential reach;
- Rounded arm-tip.

Both devices are pictured below in Figure A1.

Figure A1: ENDOCUFF™ and ENDOCUFF VISION®

ENDOCUFF VISION® is available in four different sizes dependent upon the colonoscope being used. These are displayed in Table A2.

Table A2: ENDOCUFF VISION® sizes

	ENDOCUFF VISION® code
Blue	ARV110
Green	ARV120
Purple	ARV130
Orange	ARV140

The evidence included within this submission will pertain to ENDOCUFF VISION® only given that this is the only version of the device currently available within the NHS.

2.2 What is the principal mechanism of action of the technology?

As stated in Section 2.1, ENDOCUFF VISION® is a single-use, disposable medical device that fits securely around the tip of a compatible colonoscope. It is made of a soft plastic material and contains a set of flexible hinged arms that form a ring around the head of the colonoscope. During insertion, the arms of the device lie flat against the colonoscope to enable easy passage of the instrument through the colon. During withdrawal, the arms fan out. This may help the colonoscopist to:

- Visualise lesions that may be located on the proximal side of colonic folds (i.e. the side of the fold not exposed to the lumen);
- Keep the colonoscope centred within the lumen to provide a panoramic view of the colon;
- Control withdrawal to avoid sudden slip back and ensure the complete mucosal surface is examined;
- Control the tip of the colonoscope to support therapeutic procedures such as polypectomy, endoscopic mucosal resection (EMR) and scar tissue assessment;
- Manage/straighten out loops during examination.

3 Clinical Context

3.1 Provide a brief overview of the disease or condition for which the technology is being considered in the scope issued by NICE.

Using ENDOCUFF VISION® as an add-on device in patients undergoing colonoscopy aims to improve the rate of detection (and therefore removal) of polyps, notably adenomas and allow earlier detection of carcinomas through improved detection. Adenomas left undetected can, over time, become cancerous with the patient developing colorectal cancer. Colorectal cancer (CRC) is the 4th most common cancer in the UK, with around 41,000 people being diagnosed each year (Cancer Research UK 2015). The incidence of CRC increases with age, with a sharp increase in incidence from the age of 50-54 years and the highest rates being observed in men aged 80-85 years (Cancer Research UK 2015). Patients diagnosed with CRC will be staged, typically using Dukes' classification system. Both burden of disease and risk of mortality are dependent on the stage of CRC at diagnosis, with five-year survival varying from 95% for men and 100% for women at Dukes A to around 5% for men and 10% for women at Dukes D (Cancer Research UK 2015).

The National Schedule of Reference Costs reported that 455,429 patients underwent a colonoscopy in 2015/16. This is broken down into the categories shown in Table A3. It is possible that these numbers include patients outside of the scope of this submission, i.e. people having a colonoscopy who do not have suspected CRC.

Table A3: Colonoscopy activity

Code	Description	Activity
FZ51Z	Diagnostic Colonoscopy, 19 years and over	170,286
FZ52Z	Diagnostic Colonoscopy with Biopsy, 19 years and over	158,859
FZ53Z	Therapeutic Colonoscopy, 19 years and over	126,284

3.2 Give details of any relevant NICE or other national guidance or expert guidelines for the condition for which the technology is being used. Specify whether the guidance identifies specific subgroups and make any recommendations for their treatment. If available, these should be UK based guidelines.

There are a number of guidelines relevant to people undergoing colonoscopic investigation. These are reported below.

NHS Bowel Cancer Screening Programme (BCSP)

The NHS BCSP recommends that all men and women aged 60 to 74 should be offered bowel cancer screening every 2 years. This screening currently involves a faecal occult blood sampling test. Those people with abnormal results should be offered a colonoscopy. Bowel scope screening is also being rolled out to all men and women in England who are aged 55 years (Public Health England 2015).

NICE clinical guideline (CG) 118

A NICE clinical guideline was published on colonoscopic surveillance for preventing colorectal cancer in adults with ulcerative colitis, Crohn's disease or adenomas in March 2011 (National Institute for Health and Care Excellence 2011b). Within this guidance, colonoscopic surveillance is recommended for people with adenomas. The frequency of surveillance depends upon the risk of developing colorectal cancer the patient is considered to be at. Patients are categorised into the following:

- Low risk = one or two adenomas smaller than 10mm;
- Medium risk = three or four adenomas smaller than 10 mm or one or two adenomas if one is 10 mm or larger;
- High risk = five or more adenomas smaller than 10 mm or three or more adenomas if one is 10 mm or larger (National Institute for Health and Care Excellence 2011b).

The surveillance strategy is dependent upon risk type and shown in Figure A2.

Figure A2: CG118 surveillance strategy (National Institute for Health and Care Excellence 2011b)

1.1.9 Offer the appropriate colonoscopic surveillance strategy to people with adenomas based on their risk of developing colorectal cancer as determined at initial adenoma removal (see table 2).

- Low risk: consider colonoscopy at 5 years:
  - if the colonoscopy is negative (that is, no adenomas are found) stop surveillance
  - if low risk, consider the next colonoscopy at 5 years (with follow-up surveillance as for low risk)
  - if intermediate risk, offer the next colonoscopy at 3 years (with follow-up surveillance as for intermediate risk)
  - if high risk, offer the next colonoscopy at 1 year (with follow-up surveillance as for high risk).
- Intermediate risk: offer colonoscopy at 3 years:
  - if the colonoscopy is negative, offer the next colonoscopy at 3 years. Stop surveillance if there is a further negative result
  - if low or intermediate risk, offer the next colonoscopy at 3 years (with follow-up surveillance as for intermediate risk)
  - if high risk, offer the next colonoscopy at 1 year (with follow-up surveillance as for high risk).
- High risk: offer colonoscopy at 1 year.
  - if the colonoscopy is negative, or low or intermediate risk, offer the next colonoscopy at 3 years (with follow-up surveillance as for intermediate risk)
  - if high risk, offer the next colonoscopy at 1 year (with follow-up surveillance as for high risk).

NICE CG 131

NICE guidelines were published in November 2011 around the diagnosis and management of colorectal cancer. Within these guidelines colonoscopies are recommended to confirm the diagnosis of colorectal cancer in patients without major comorbidities. In addition, surveillance colonoscopies are recommended in patients treated for colorectal cancer. These surveillance colonoscopies should be conducted 1 year after an apparently curative resection and, if normal, again after 5 years (National Institute for Health and Care Excellence 2011a).

NICE Guideline (NG) 12 - Suspected cancer: recognition and referral

NG 12, published in 2015, on recognition and referral for suspected cancer recommends that people with suspected CRC should typically be referred for a suspected cancer pathway referral within two weeks.

The British Society of Gastroenterology (BSG) and the Association of Coloproctology for Great Britain and Ireland (ACPGBI) guidelines for colorectal cancer screening and surveillance in moderate and high risk groups

The BSG/ACPGBI guideline, published in 2010, provides guidance on "the appropriateness, method and frequency of screening for people at moderate and high risk from colorectal cancer." The guidance is largely focused on subgroups of patients with specific risk factors indicating that they are at high risk of colorectal cancer. Information on the surveillance schedule following detection is provided and is displayed in Figure A3 (Cairns et al. 2010).

Figure A3: BSG/ACPGBI guideline: surveillance following detection of colorectal adenomas

Risk of colorectal cancer or advanced adenomas (≥1 cm as measured at endoscopy or high-grade dysplasia)

- Patients with only one or two small (<1 cm) adenomas are at low risk, and need no colonoscopic surveillance or 5-yearly until one negative examination then cease surveillance. **Recommendation grade: B**
- Patients with three or four small adenomas or at least one adenoma ≥1 cm are at intermediate risk and should be screened 3-yearly until two consecutive examinations are negative. **Recommendation grade: B**
- If either of the following is detected at any single examination (at baseline or follow-up): five or more adenomas, or three or more adenomas at least one of which is ≥1 cm, the patient is at high risk and an extra examination should be undertaken at 12 months before returning to 3-yearly surveillance. **Recommendation grade: B**

Patients can be offered surveillance until age 75 years and thereafter continue depending on relative cancer risk and co-morbidity. Colonoscopy is likely to be less successful and more risky at older ages. Further, the average lead time for progression of an adenoma to cancer is 10 years which is of the same order as the average life expectancy of an individual aged 75 years or older, suggesting that most will not benefit from surveillance. **Recommendation grade: B**

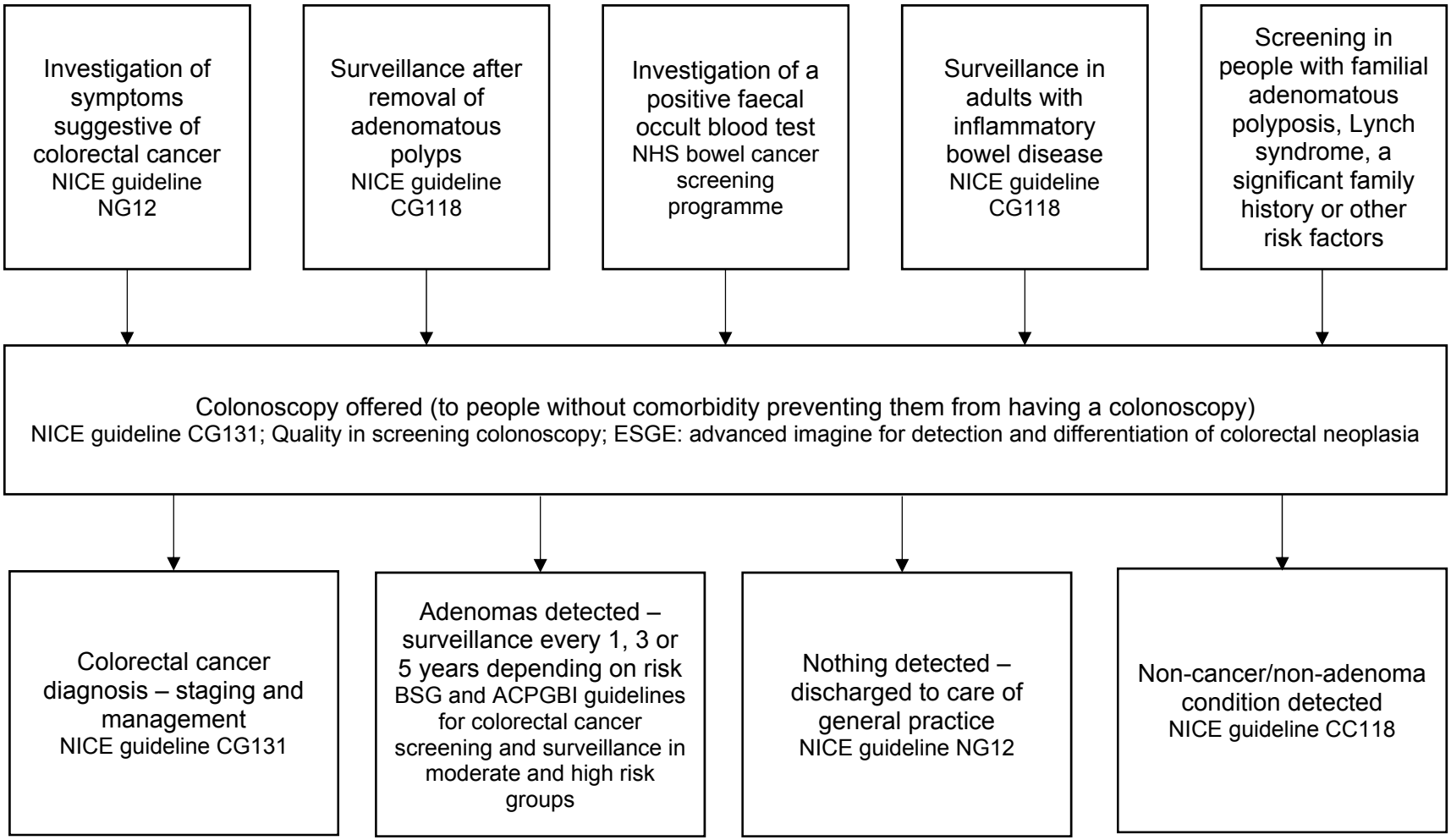
These guidelines are based on accurate detection of adenomas, otherwise risk status will be underestimated. Patients with a failed colonoscopy, for whatever reason, should undergo repeat colonoscopy or an alternative complete colonic examination. **Recommendation grade: B**

The site of large sessile adenomas removed piecemeal should be re-examined at 2–3 months. Small areas of residual polyp can then be treated endoscopically, with a further check for complete eradication in 2–3 months. India ink tattooing aids recognition of the polypectomy site at follow-up. If extensive residual polyp is seen, surgical resection needs to be considered, or alternatively referral to a colonoscopist with special expertise in advanced polypectomy techniques. If there is complete healing of the polypectomy site, then there should be a colonoscopy at 1 year, to check for missed synchronous polyps, before returning to 3-yearly surveillance. **Recommendation grade: B**

3.3 Describe the clinical pathway of care that includes the proposed use of the technology.

An overview of the care pathway is shown in Figure A4. This diagram has been taken and adapted from a recent NICE scope for the assessment of virtual chromoendoscopy for real-time assessment of colorectal polyps during colonoscopy (National Insitute for Health and Care Excellence 2016). Patients with incomplete colonoscopies should be offered a repeat colonoscopy with consideration of a more experienced operator conducting this (National Institute for Health and Care Excellence 2011b).

Figure A4: Overview of Care Pathway



ENDOCUFF VISION® may be used in patients undergoing colonoscopy as shown in Figure A3 above. The population included within the scope is people undergoing colonoscopy for suspected bowel cancer or for the removal of known polyps. People with suspected bowel cancer are likely to derive either from those with symptoms suggestive of CRC or those within a screening programme that have had a positive faecal occult blood test or have risk factors. Patients with known polyps requiring removal may derive from any of the categories shown above.

The use of ENDOCUFF VISION® in the standard pathway of care is an add-on to colonoscopy and therefore does not replace any existing technology. Using ENDOCUFF VISION® during a colonoscopy should help to detect, and thus remove, a greater number of cancerous and pre-cancerous polyps. This may avoid the need for treatment of more advanced cancer at a later stage. An increase in ADR by 1% is associated with a 3% decrease in the risk of cancer (hazard ratio, 0.97; 95% confidence interval: 0.96 to 0.98) (Corley et al. 2014a). Increased visualisation would lead to increased detection (and potential removal) of adenomas during colonoscopy or CRC detection especially at an early stage. The increase in detection of adenomas may result in more people requiring colonoscopies for surveillance purposes in subsequent years.

3.4 Describe any issues relating to current clinical practice, including any uncertainty about best practice.

The clinical pathway of care described in Section 3.3 is consistent with NICE clinical guidelines; therefore, there are no known issues relating to current clinical practice.

3.5 Describe the new pathway of care incorporating the new technology that would exist if the technology was adopted by the NHS in England.

ENDOCUFF VISION® can be readily adopted into the pathway of care as an add-on device used during colonoscopies. The pathway of care would remain as shown in Figure A3.

3.6 Describe any changes to the way current services are organised or delivered as a result of introducing the technology.

No changes are anticipated.

3.7 Describe any additional tests or investigations needed for selecting or monitoring patients, or particular administration requirements, associated with using this technology that are over and above usual clinical practice.

No additional tests are required to select patients for use with ENDOCUFF VISION®. Where more patients have adenomas identified or carcinomas detected additional patients will require either surveillance or treatment for CRC at a potentially earlier stage.

3.8 Describe any additional facilities, technologies or infrastructure that need to be used alongside the technology under evaluation for the claimed benefits to be realised.

None are anticipated.

3.9 Describe any tests, investigations, interventions, facilities or technologies that would no longer be needed with using this technology.

ENDOCUFF VISION® may allow for earlier diagnosis of CRC (through detection of carcinomas) or avoidance of cancer (through removal of adenomas which may otherwise in time become cancerous). The earlier diagnosis or avoidance of CRC may reduce or remove the costs associated with its treatment.

3.10 Describe how the NHS in England can disinvest from tests, investigations, interventions, facilities or technologies described in section 3.9 that would no longer be needed with using this technology.

The treatment of CRC may comprise of chemotherapy, radiotherapy, surgery or a combination of modalities. Treatment of fewer patients with CRC or patients at an earlier stage requiring less intensive treatment, will allow these therapeutic resources to be used elsewhere. However, increasing adenoma detection may lead to a higher surveillance burden, resulting in more colonoscopies being conducted.

4 Regulatory Information

4.1 Provide PDF copies of the following documents:

- Instructions for use;
- Ce mark certificate or equivalent uk regulatory approval such as ec declaration of conformity;
- Quality systems (iso 13485) certificate (if required).

PDF copies of these documents should be submitted at the same time as section A.

PDF copies of these documents are attached.

4.2 Does the technology have CE mark for the indication(s) specified in the scope issued by NICE? If so, give the date that authorisation was received. If not, state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

Yes, ENDOCUFF VISION® has a CE mark for the indication within the scope. This authorisation was received in August 2016.

4.3 Does the technology have regulatory approval outside the UK? If so, please provide details.

The Boddingtons' CE mark is valid throughout EU, Norway, Switzerland, Liechtenstein, Iceland (EFTA). The product is also available in the USA, Australia and New Zealand.

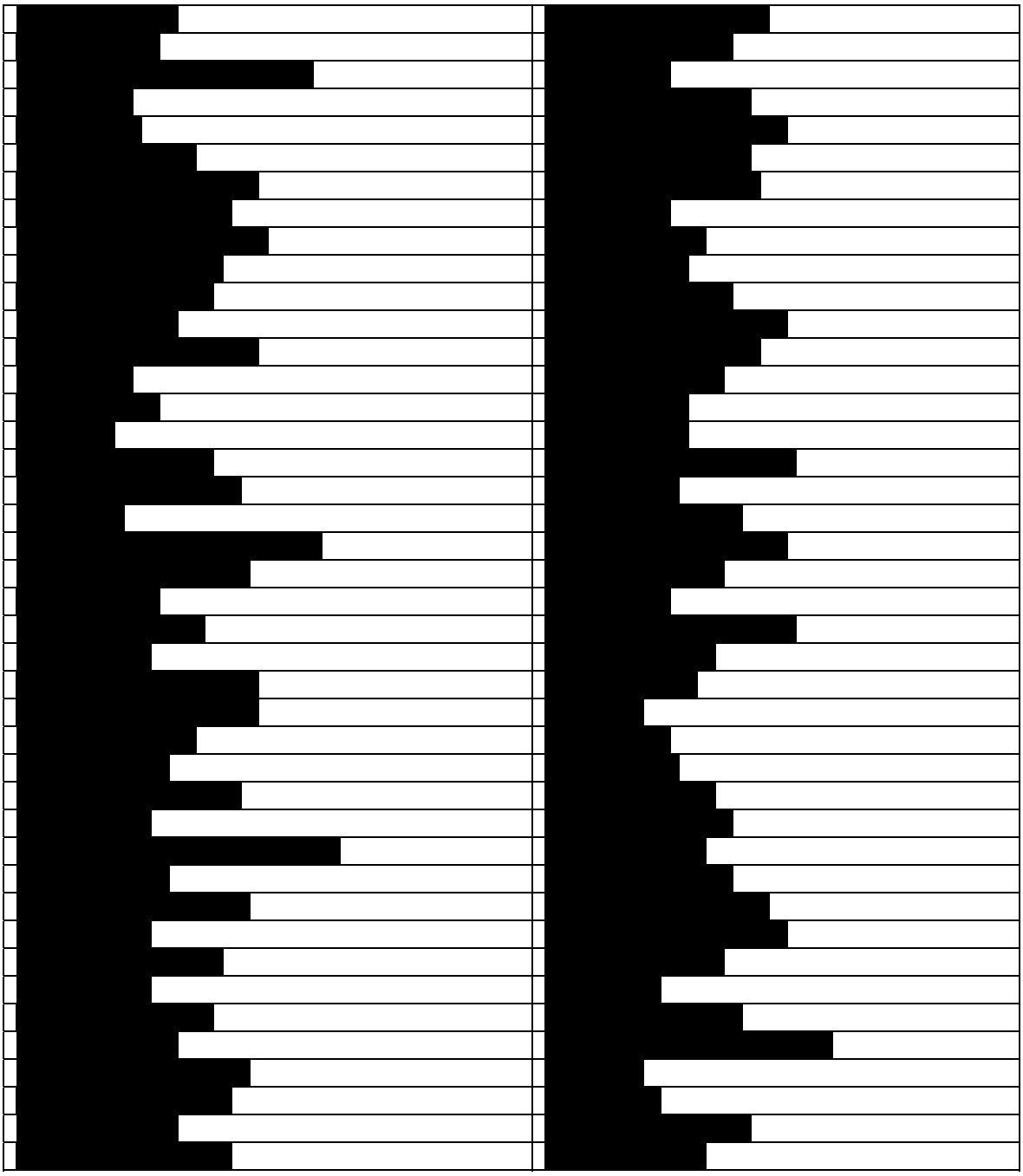
4.4 If the technology has not been launched in the UK provide the anticipated date of availability in the UK.

Not applicable as ENDOCUFF VISION® has been launched within the UK.

4.5 If the technology has been launched in the UK provide information on the use in England.

ENDOCUFF VISION® became commercially available in the UK in October 2014. The following NHS Trusts listed in Table A3 have *ordered* ENDOCUFF VISION®. However, it should be noted that it is not known whether these Trusts are actually using the device:

Table A4: NHS Trusts that have ordered ENDOCUFF VISION®



5 Ongoing Studies

5.1 Provide details of all completed and ongoing studies on the technology from which additional evidence relevant to the decision problem is likely to be available in the next 12 months.

Table A5 shows the ongoing studies identified through the searches described in detail in Section B. The status of many of the trials on clinicaltrials.gov is not current, hence a column has been included to provide an update on the true status of the trial as far is known.

Table A5: Ongoing ENDOCUFF VISION® studies

Trial ID	Full record	Intervention	Clinical Trials Status
NCT03418948 2017	Radboud University. (2017). Comparison of AMR and ADR between Endocuff vision-assisted and conventional colonoscopy: a multicenter randomized trial (EXCEED). Bethesda: US National Library of Medicine. Available from https://clinicaltrials.gov/ct2/show/NCT03418948. Identifier: NCT03418948	ENDOCUFF VISION®	Recruiting
NCT03398447 2018	New York University School of Medicine. (2018). High-definition white-light colonoscopy versus high-definition white-light colonoscopy with Endocuff vision for Endpoints of procedural times, 40 Years. Bethesda: US National Library of Medicine. Available from https://clinicaltrials.gov/ct2/show/NCT03398447. Identifier: NCT03398447	ENDOCUFF VISION®	Recruiting
NCT03361917 2017	Indiana University. (2017). Standard colonoscopy versus colonoscopy with Endocuff vision, 40 Years. US National Library of Medicine: Bethesda. Available from https://clinicaltrials.gov/ct2/show/NCT03398447. Identifier: NCT03361917	ENDOCUFF VISION®	Recruiting
NCT03344055 2017	Société Française d'Endoscopie Digestive. (2017). Endocuff-assisted colonoscopy vs standard colonoscopy on adenoma detection rate, 18 Years. Bethesda: US National Library of Medicine. Available from: https://clinicaltrials.gov/ct2/show/NCT03361917. Identifier: NCT03344055	ENDOCUFF VISION®	Recruiting
NCT03117114 2017	Technische Universität München. (2017). Endocuff vision assisted vs. standard polyp resection in the colorectum, 18 Years. Bethesda: US National Library of Medicine. Available from: https://clinicaltrials.gov/ct2/show/NCT03117114. Identifier: NCT03117114	ENDOCUFF VISION®	Not yet recruiting

Trial ID	Full record	Intervention	Clinical Trials Status
NCT03072472 2017	South Tyneside NHS Foundation Trust. (2017). BowelScope: accuracy of detection using Endocuff optimisation of mucosal abnormalities, 55 Years. Bethesda: US National Library of Medicine. Available from: https://clinicaltrials.gov/ct2/show/NCT03117114. Identifier: NCT03072472	ENDOCUFF VISION®	Recruiting
ACTRN12617001364369 2017	Box Hill Hospital Victoria. (2017). Endocuff-vision assisted chromoendoscopy for surveillance for cancer and dysplasia in inflammatory bowel disease, 18 Years. Sydney: National Health and Medical Research Council (NHMRC) Clinical Trials Centre - University of Sydney. Available from: https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=373642. Identifier: ACTRN12617001364369	ENDOCUFF VISION®	Recruiting
Fang 2017	Fang W, Haridy J, Keung C, et al. (2017) Endocuff vision-assisted colonoscopy for surveillance of cancer and dysplasia in ulcerative colitis. Journal of Gastroenterology and Hepatology (Australia) 32(Suppl 2),pp. 22.	ENDOCUFF VISION®	Unknown
Jacob 2017	Jacob A and Hewett P (2017) Comparing standard colonoscopy to Endocuff vision assisted colonoscopy: a randomized control trial with video analysis. Diseases of the Colon & Rectum 60(6),pp. E463-E464.	ENDOCUFF VISION®	Expected to complete in Jan 2017 but not further information available

5.2 If the technology is, or is planned to be, subject to any other form of assessment in the UK, please give details of the assessment, organisation and expected timescale.

No other assessments within the UK are either planned or ongoing.

6 Equality

NICE is committed to promoting equality of opportunity and eliminating unlawful discrimination on the grounds of age, disability, gender reassignment, race, religion or belief, sex, and sexual orientation, and to comply fully with legal obligations on equality and human rights.

Equality issues require special attention because of NICE's duties to have due regard to the need to eliminate unlawful discrimination, promote equality and foster good relations between people with a characteristic protected by the equalities legislation and others.

Any issues relating to equality that are relevant to the technology under assessment should be described. This section should identify issues described in the scope and also any equality issues not captured in the final scope.

Further details on equality may be found in Section 11.3 of this document.

6.1.1 Describe any equality issues relating to the patient population and condition for which the technology is being used.

ENDOCUFF VISION® should not be used in people who cannot have colonoscopies, including those with colonic strictures, known diverticular disease and known acute colitis.

6.1.2 Describe any equality issues relating to the assessment of the technology that may require special attention.

No issues requiring special attention have been identified.

6.1.3 How will the submission address these issues and any equality issues raised in the scope?

People in whom colonoscopies are counter indicated are not included within the evidence incorporated within this submission.

Section B – Clinical Evidence

7 Published and Unpublished Clinical Evidence

Section B requires sponsors to present published and unpublished clinical evidence for their technology.

Sponsors should read Section 6 of the Medical Technologies Evaluation Programme methods guide on published and unpublished evidence, available from www.nice.org.uk/mt

All statements should be evidence-based and directly relevant to the scope. Reasons for deviating from the scope should be clearly stated and explained in Table A1.

Sponsors are required to submit section B in advance of the full submission (for details on timelines, see the NICE document 'Guide to the Medical Technologies Evaluation Programme process', available from www.nice.org.uk/mt

7.1 Identification of Studies

Published studies

7.1.1 Describe the strategies used to retrieve relevant clinical data from the published literature. Exact details of the search strategy used should be provided in Section 10, Appendix 1.

A literature search was designed in Ovid MEDLINE to identify studies reporting on the use of ENDOCUFF™ or ENDOCUFF VISION® in the context of colonoscopy. Strategy development was informed by the search methods described in the Cochrane Handbook and the Centre for Reviews and Dissemination (CRD) guidance.

The strategy comprised only two concepts to maximise sensitivity: the intervention (ENDOCUFF™ or ENDOCUFF VISION®) and the population (colonoscopy). This approach also ensured that a single strategy could be used to identify both clinical and economic evidence.

The search strategy was devised using a combination of subject indexing terms and free text search terms in the title, abstract and “keyword heading word” fields. The search terms were identified through discussion within the research team, scoping searches, browsing database thesauri, and use of the PubMed PubReMiner tool (http://hgserver2.amc.nl/cgi-bin/miner/miner2.cgi [accessed 2018 21st March]). Before running the final searches, the sensitivity of the strategy was tested by checking retrieval against a sample of relevant clinical studies known to the sponsor. The draft strategy successfully retrieved all studies which were present in MEDLINE or MEDLINE In-Process.

A multi-stranded search approach was employed:

1. To maximise sensitivity, the device name and the names of the manufacturer and distributor were conducted as stand-alone searches and were not combined with the population concept (search lines 1-6, see Appendix 10.1.4 MEDLINE strategy).

2. In addition a broader set of search terms were then used to capture relevant records where ENDOCUFF™ or ENDOCUFF VISION® may not have been explicitly named in the title, abstract or keyword heading fields (search lines 7-23, see Appendix 10.4 MEDLINE strategy). This comprised free text and subject indexing terms to describe the population such as colonoscopy, bowel screening, or bowel cancer diagnoses. These were combined with free text search terms to describe the intervention such as cap, cuff, or tip, using the Boolean AND or proximity operators. Free text terms to capture the intervention also included those that describe the novel aspects of the ENDOCUFF™ and ENDOCUFF VISION® device such as the flexible or retractable arms. The search terms used for the intervention concept used free text terms only, because at that time of the search there were no Medical Subject Headings (MeSH) specific to ENDOCUFF™ or ENDOCUFF VISION®.

The Ovid MEDLINE strategy excluded animal studies using a standard algorithm. The strategy was not limited by language or publication type. Based on the earliest availability of the ENDOCUFF™, the search was limited to records with a publication date of 2010 or later.

The MEDLINE strategy was translated appropriately for each of the databases searched. The search was conducted in a range of relevant databases of published research including those databases specified as a minimum in Section 10.1 of the NICE MTEP Sponsor Submission Template:

- MEDLINE including MEDLINE In-Process (Ovid)
- Embase (Ovid)
- The Cochrane Library (Wiley):
    - Cochrane Database of Systematic Reviews (CDSR)
    - Cochrane Central Register of Controlled Trials (CENTRAL)
    - Database of Abstracts of Reviews of Effects (DARE)

- Health Technology Assessment Database (HTA Database);
- NHS Economic Evaluation Database (NHS EED)

The reference lists of relevant papers were also checked to identify any additional studies that may have been missed by database searches.

The titles and abstracts of bibliographic records were downloaded and imported into EndNote bibliographic management software and duplicate records were removed using several algorithms.

Unpublished Studies

7.1.2 Describe the strategies used to retrieve relevant clinical data from unpublished sources.

We searched for unpublished evidence that had been presented at relevant conferences or meetings. We searched Embase, which indexes the proceedings of the conferences identified by the research team as most likely to yield relevant studies:

- Digestive Disease Week
- American College of Gastroenterology Annual Scientific Meeting
- British Society of Gastroenterology Annual Meeting
- United European Gastroenterology Week

The most recent proceedings (2014-2018) of each conference were checked to ensure that they were included within Embase at the time of the searches. Proceedings of the British Society of Gastroenterology Annual Meetings 2015-2017, American College of Gastroenterology Annual Scientific Meeting 2016-2017, Digestive Disease Week 2017, and United European Gastroenterology Week 2016-2017 were not included in Embase and so were searched by hand via each organisation's webpage.

We also searched the Conference Proceedings Citation Index – Science (Web of Knowledge) for further evidence from conferences or meetings.

The FDA webpages (http://www.fda.gov/) were searched to identify any unpublished evidence that may have formed part of a regulatory submission.

The following clinical trial registries were searched to identify any ongoing, recently completed, or other unpublished research:

- Clinicaltrials.gov (https://clinicaltrials.gov/)
- WHO ICTRP search portal (http://apps.who.int/trialsearch/)
- UK Clinical Trials Gateway (https://www.ukctg.nihr.ac.uk/)

Supplementary search approaches were undertaken involving checking the reference lists of published studies relating to ENDOCUFF™ and ENDOCUFF VISION® and requesting evidence from the manufacturer.

Supplementary search approaches were undertaken involving checking the reference lists of published studies relating to ENDOCUFF™ and ENDOCUFF VISION® and requesting evidence from the manufacturer.

The search was conducted in December 2016, and update searches were carried out in January 2017 and February 2018. The PRISMA diagram shows the results from both the original searches and the updates, which were deduplicated against each other. The full search strategies for all sources (including search dates and result numbers) are included in Appendices 10.1.4.

The combined searches for published clinical evidence, unpublished clinical evidence, and economic evidence retrieved 12,444 records. After duplicates were removed, 3,497 unique records remained for assessment.

7.2 Study Selection

Published studies

7.2.1 Complete table B1 to describe the inclusion and exclusion criteria used to select studies from the published literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

Table B1 shows the eligibility criteria used to select studies. Although the search was designed to capture studies of both ENDOCUFF™ and ENDOCUFF VISION®, only studies of ENDOCUFF VISION® were of interest to the current review.

Table B1: Eligibility criteria used to select studies

Inclusion criteria	
Population	Studies of adult (over 18 years of age) patients scheduled for colon screening, colonic surveillance or diagnostic colonoscopy, for any reason.
Interventions	Studies that evaluate ENDOCUFF VISION® –assisted colonoscopies.
Comparators	Standard colonoscopies (i.e. colonoscopies with no distal device attached).
Outcomes	Studies that report data on one or more of the following clinical or safety outcomes: • Detection rate: o Benign polyps (types, location); o Adenoma (ADR) (types, location, definition used at each stage); o Cancers. • Device insertion and withdrawal time; • Duration of colonoscopy; • Caecal intubation rate (CIT); • Mean number of adenomas per patient (MAP); • Miss rate (where recorded); • Outcomes relating to patients' comfort and satisfaction; • Complications, including: o Removal of device due to patient issues; o Device retrieval if detached from scope. • Adverse events, including: o Bowel perforation; o Mucosal petechiae/ scratches; o Anal discomfort. • Long term outcomes (Protocol Amendment (PA)1[1]) o Incidence of subsequent interval cancers; o Referral rates for specialist treatment and rates of subsequent surgery, chemotherapy and radiotherapy; o Tumour recurrence after colonoscopic resection; o Rate of repeat colonoscopy after electrocoagulation for angiodysplasia.

[1] PA1- additional outcomes following receipt of the NICE draft scope.

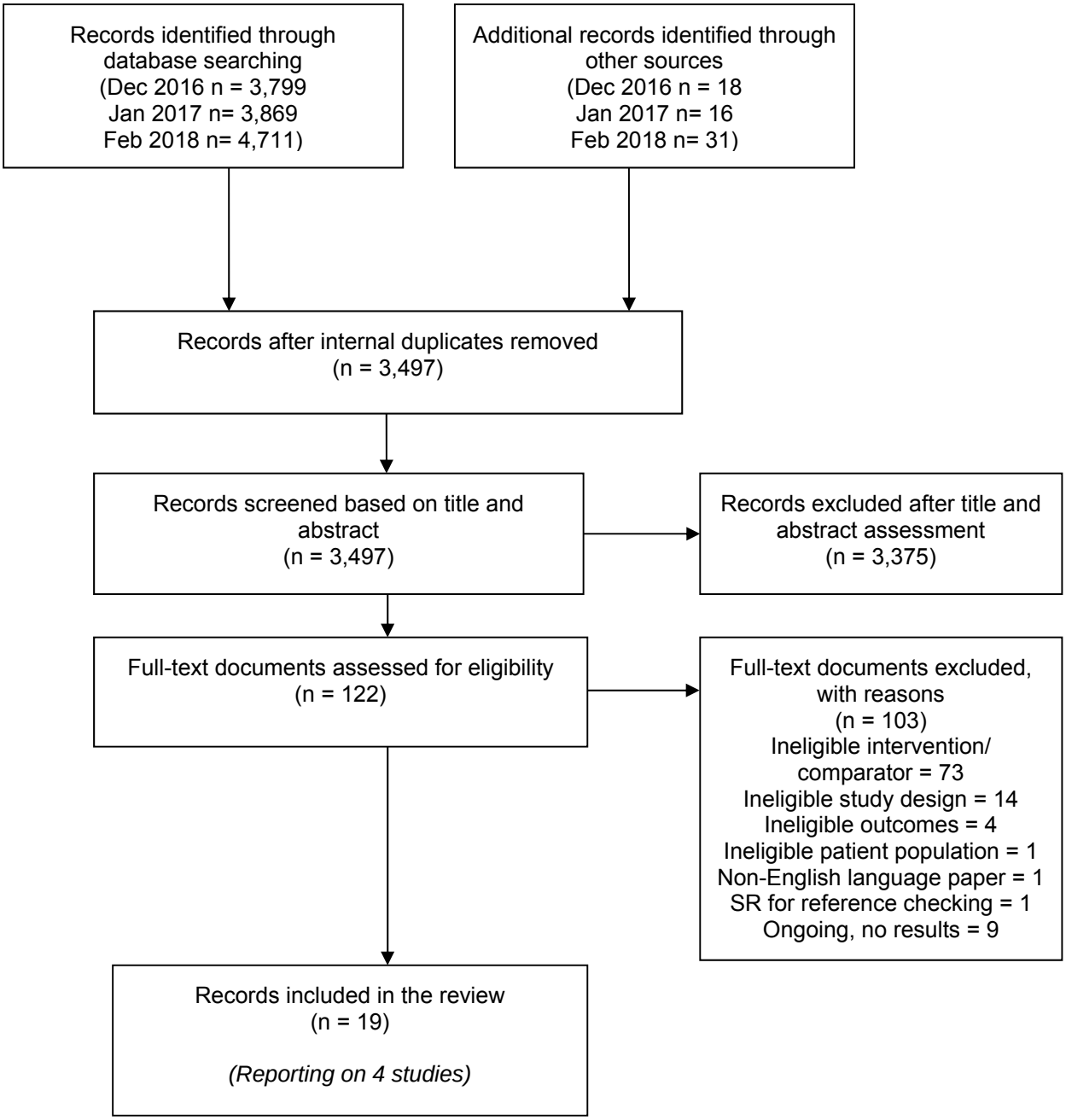
Inclusion criteria	
Study design	• Randomised controlled trials (RCTs) of any size and duration; • Non-randomised comparative and uncontrolled studies, which report relevant clinical effectiveness or safety data for ENDOCUFF VISION®; • Non comparative or single arm studies, which provide relevant safety data; • Studies published as abstracts or conference presentations will be eligible if adequate data are provided; • Systematic reviews as a source of references to relevant primary studies.
Language restrictions	• No language limits (although studies reported in languages other than English would not be extracted, but would be listed for information only).
Search dates	• 2010 to the current date.
Exclusion criteria	
Population	Studies of patients under the age of 18 years or of adult patients who are not scheduled for colon screening, colon surveillance or diagnostic colonoscopy for reason.
Interventions	Studies that do not evaluate ENDOCUFF VISION®–assisted colonoscopies.
Outcomes	Studies that do not report data on one or more of the outcomes listed in the inclusion criteria.
Study design	Any study design that is not listed in the inclusion criteria.
Language restrictions	N/A
Search dates	

7.2.2 Report the numbers of published studies included and excluded at each stage in an appropriate format.

A total of 3,497 records were screened for relevance, based on their title and abstract, by two reviewers independently. Disagreements were resolved by a third reviewer. 3,375 records were excluded based on title and abstract screening and 122 full text reports were assessed for relevance against the pre-defined eligibility criteria. 103 of the 122 full text records were excluded and 19 records, reporting on 4 studies, were included in the review (see Table B3). Of these, 3 studies had an associated full-text publication.

The full record selection process for this review is presented as a PRISMA flow diagram in Figure B1.

Figure B1: Record selection process (PRISMA flow diagram)



N - number of records; PRISMA- Preferred reporting Items for Systematic Reviews and Meta-analyses; SR- systematic review.

Unpublished studies

7.2.3 Complete table B2 to describe the inclusion and exclusion criteria used to select studies from the unpublished literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

The same eligibility criteria, presented in Table B1, were used to assess unpublished literature.

7.2.4 Report the numbers of unpublished studies included and excluded at each stage in an appropriate format.

One unpublished study (Rameshshanker 2016) reported in a conference abstract only was included (Rameshshanker et al. 2016).

7.3 Complete List of Relevant Studies

The sponsor should provide a PDF copy of all studies included in the submission if the sponsor is either the copyright owner or has adequate copyright clearance to permit the intended use by NICE. If the sponsor does not have sufficient copyright clearance, they are asked to submit references or links only, or details of contacts for unpublished studies. For unpublished studies for which a manuscript is not available, provide a structured abstract about future journal publication. If a structured abstract is not available, the sponsor must provide a statement from the authors to verify the data provided.

7.3.1 Provide details of all published and unpublished studies identified using the selection criteria described in Tables B1 and B2.

Table B2 shows the complete list of relevant published and unpublished studies identified (Ngu et al. 2018a, Bhattacharyya et al. 2017, Tsiamoulos et al. 2018, Rameshshanker et al. 2016). For three of the studies, a full text publication in a peer reviewed journal as well as several related conference abstracts were identified. In these cases, the full text publication was

considered to be the ‘primary’ publication and the conference abstracts are listed as associated publications.

For one of these studies, Tsiamoulos 2018, all of the associated abstracts reported interim data for fewer patients than reported in the full text publication. Results were extracted from the full text publication only, but associated publications are listed in Table B2 for information.

For one study, data were only available in a conference abstract .

Table B2*:* **Relevant published and unpublished studies**

Study name (acronym)	Primary study reference	Associated records	Population	Intervention	Comparator
ADENOMA	Ngu WS, Bevan R, Tsiamoulos ZP, et al. Gut 2018;66:1–9.	Bevan R, Ngu W, Saunders B, Tsiamoulos Z, Bassett P, Hoare Z, et al. The ADENOMA Study. Accuracy of detection using Endocuff Vision™ optimization of mucosal abnormalities: study protocol for randomized controlled trial. Endosc Int Open. 2016;4(2):E205-E12. (Bevan et al. 2016) Ngu WS, Bevan R, Tsiamoulos ZP, Bassett P, Hoare Z, Rutter M, et al. Improving colorectal adenoma detection rate with Endocuff vision. Results of the adenoma randomised controlled trial. Gastroenterology. 2017;152(5 Suppl 1):S1313-S14. Ngu W, Bevan R, Panagiotis Z, Bassett P, Hoare Z. Improved adenoma detection with Endocuff-Vision™ - a multi-centre randomised controlled trial. In: United European Gastroenterology Week, Vienna; 15-19 October. 2016. (Ngu et al. 2016) South Tyneside NHS Foundation Trust. Accuracy of detection using Endocuff optimisation of mucosal abnormalities. Identifier: NCT02552017. In: ClinicalTrials.gov. [internet]. Bethesda: US National Library of Medicine: 2015. Available from https://clinicaltrials.gov/show/NCT02552017. (South Tyneside NHS Foundation Trust 2015)	Patients aged older than 18 years were referred for colonoscopy as part of a postpolypectomy surveillance programme or with positive faecal occult blood test as part of the bowel cancer screening program	ENDOCUFF VISION®	Standard colonoscopy
E-Cap	Bhattacharyya R, Chedgy F, Kandiah K, Fogg C, Higgins B, Haysom-Newport B, *et al.* Endocuff-assisted vs standard colonoscopy in the fecal occult blood test-based UK bowel cancer screening programme	Bhattacharyya R, Chedgy F, Kandiah K, Fogg C. The first randomised controlled trial of endocuff vision® assisted colonoscopy versus standard colonoscopy for polyp detection in bowel cancer screening patients (E-CAP study). In: United European Gastroenterology Week, Vienna; 15-19 October. 2016. (Bhattacharyya et al. 2016a)	Patients aged 60-75 years undergoing screening colonoscopy	ENDOCUFF VISION®	Standard colonoscopy

Study name (acronym)	Primary study reference	Associated records	Population	Intervention	Comparator
	(E-cap study): a randomized trial. Endoscopy. 2017;49(11):1043-50.	Bhattacharyya R, Chedgy F, Longcroft-Wheaton G, Bhandari A. The first randomised controlled trial of Endocuff vision® assisted colonoscopy versus standard colonoscopy for polyp detection in bowel cancer screening patients (E-Cap Study). In: British Society of Gastroenterology Annual General Meeting, London; 20–23 June. 2016. PTH-039 (Bhattacharyya et al. 2016c) Bhattacharyya R, Chedgy F, Kandiah K, Gadeke L, Higgins B, Fogg C, et al. The first randomised controlled trial of Endocuff vision assisted colonoscopy versus standard colonoscopy for polyp detection in bowel cancer screening patients (E-CAP study). Gastroenterology. 2016;150(4 Suppl 1):S1270. (Bhattacharyya et al. 2016b) Portsmouth Hospitals NHS Trust. Endo-cuff Assisted Vs. Standard Colonoscopy for Polyp Detection in Bowel Cancer Screening. Identifier: NCT02529007. In: ClinicalTrials.gov. [internet]. Bethesda: US National Library of Medicine: 2015. Available from https://clinicaltrials.gov/show/NCT02529007. (Portsmouth Hospitals NHS Trust 2015)			
Tsiamoulos 2018	Tsiamoulos ZP, Misra R, Rameshshanker R, Elliott TR, Beintaris I, Thomas-Gibson S, *et al.* Impact of a new distal attachment on colonoscopy performance in an academic screening center. Gastrointest Endosc. 2018;87(1):280-87.	Tsiamoulos ZP, Misra R, Bourikas LA, Rajaratnam R, Patel KP, Thomas-Gibson S, et al. Endocuff-vision: impact on colonoscopist performance during screening. Gastrointestinal Endoscopy. 2015;81(5 Suppl):AB209. **Interim data only** (Tsiamoulos et al. 2015a) Elliott T, Tsiamoulos Z, Haycock A, Bourikas L, Patel K, Misra R, et al. Endocuff-vision: impact on colonoscopist performance during screening. J Gastroenterol Hepatol (Aus). 2015;3):36. **Interim data only**	Patients undergoing screening colonoscopy	ENDOCUFF VISION®	Standard colonoscopy

Study name (acronym)	Primary study reference	Associated records	Population	Intervention	Comparator
		Tsiamoulos ZP, Misra R, Kinesh P, Haycock A, Suzuki N, Thomas-Gibson S*, et al.* Endocuff-vision: Impact on colonoscopist performance during screening. United European Gastroenterol J. 2015;1:A563.			
		Tsiamoulos ZP, Misra R, Patel K, Bourikas L, Thomas-Gibson S, Haycock A, et al. Endocuff-vision™: impact on colonoscopist performance during screening. Gut. 2015;64(Suppl 1):A376. **Interim data only** (Tsiamoulos et al. 2015c)			
		Tsiamoulos ZP, Patel K, Elliott T, Misra R, Thomas-Gibson S, Fraser C, et al. Does Endocuff-vision improve adenoma detection? Gut. 2014;63(Suppl 1):A152-A53. **Interim data only** (Tsiamoulos et al. 2014a)			
		Tsiamoulos ZP, Patel K, Misra R, Suzuki N, Haycock A, Thomas-Gibson S, et al. Single centre pilot evaluating the use of Endocuff-vision in screening colonoscopy. United European Gastroenterology Journal. 2014;2(Suppl 2):A495. **Interim data only** (Tsiamoulos et al. 2014b)			
		Tsiamoulos ZP, Patel KP, Elliott TR, Misra R, Thomas-Gibson S, Fraser C*, et al.* Sa1494 Does Endocuff-Vision Improve Adenoma Detection Rate At Screening Colonoscopy? Gastrointest Endosc. 2014;79(5):AB233-AB34. **Interim data only** (Tsiamoulos et al.)			
Rameshshanker 2016	Rameshshanker R, Wilson A, Tsiamoulos Z, Tekkis P. Number of significant polyps detected per six minutes of withdrawal time at colonoscopy (Sp6): a new measure of	No additional publications identified	Patients aged 55 - 74 years undergoing screening colonoscopy	ENDOCUFF VISION®	Standard colonoscopy

Study name (acronym)	Primary study reference	Associated records	Population	Intervention	Comparator
	colonoscopy efficiency and quality. In: British Society of Gastroenterology Annual General Meeting, 20–23 June. 2016. PTU-030 (Rameshshanker et al. 2016)				

7.3.2 State the rationale behind excluding any of the published studies listed in Tables B3 and B4.

None of the identified studies were excluded from the review.

7.4 Summary of Methodology of Relevant Studies

7.4.1 Describe the study design and methodology for each of the published and unpublished studies using tables B5 and B6 as appropriate. A separate table should be completed for each study.

Table B3 to Table B6 below outline the design and methodology of the relevant studies.

Table B3: Summary of the methods of the randomised controlled trials: ADENOMA

Study name (acronym)	**Accuracy of Detection using Endocuff Optimisation of Mucosal Abnormalities (ADENOMA)**
Objectives	To compare the adenoma detection rate (ADR) between ENDOCUFF VISION® assisted colonoscopy and standard colonoscopy.
Location	UK (Multicentre: 1 academic and 6 community hospitals)
Design	Randomised controlled trial
Duration of study	19 months – Nov 2014 to Jun 2016 (estimated study completion date in the clinical trial record). Patient recruitment was reported in the primary publication as Nov 2014 to Feb 2016.
Sample size	1,772
Inclusion criteria	Patients aged over 18 years and referred for colonoscopy for clinical symptoms, as part of a postpolypectomy surveillance programme or with positive faecal occult blood test as part of BCSP.
Exclusion criteria	Patients were excluded if there was a pre-endoscopy suspicion of large bowel obstruction; known colon cancer or polyposis syndromes; known colonic stricture; known severe diverticular segment; known active colitis; were receiving anticoagulants which had not been stopped before the procedure (meaning polypectomy might not be undertaken); if pregnant or attending for a therapeutic procedure or assessment of a known lesion.
Method of randomisation	Patients were randomised using a computerised internet-based platform. Randomisation was stratified based on age, gender, hospital site and BCSP using a dynamic adaptive algorithm.
Method of blinding	Single blinding (outcome assessors only)
Intervention(s) (n=)	ENDOCUFF VISION® (n = 888)
Comparator(s) (n =)	Standard colonoscopy (n = 884)
Baseline differences	Patients' characteristics were comparable across both groups

Study name (acronym)	Accuracy of Detection using Endocuff Optimisation of Mucosal Abnormalities (ADENOMA)
Duration of follow-up, lost to follow-up information	21 days. No patients were lost to follow-up.
Statistical tests	A one-sided X^2 test was used to compare the primary outcome between groups. Logistic regression was used as a sensitivity analysis to re-examine group differences, adjusting for stratification factors included in the randomisation process. MAP was analysed using the Mann-Whitney U test. X^2 test and Mann-Whitney U test were used to analyse secondary outcomes where the objective was to examine the superiority of ENDOCUFF VISION®. Other secondary outcomes were examined on a non-inferiority basis. For continuous outcomes, one-sided 97.5% CI for the mean difference between groups was calculated. For binary outcomes, a one-sided 97.5% CI for the difference in proportions was calculated. Non-inferiority was assumed when the bound of the CI did not cross the prespecified point of non-inferiority. All superiority analyses were performed on an intention-to-treat (ITT) basis. Per-protocol analyses were used for outcomes analysed on a non-inferiority basis and as a sensitivity analyses for the primary outcome.
Primary outcomes	Difference in ADR between ENDOCUFF VISION®-assisted colonoscopy and standard colonoscopy.
Secondary outcomes	MAP, polyp distribution (including assessment of cancer detection), detection of sessile serrated polyps, rate of cuff exchange, CIT, insertion time to caecum, withdrawal time, patient experience, future colonoscopic workload due to increased ADR, difference in ADR between BCSP and non-BCSP colonoscopists, changes in ADR throughout the trial, colonoscopist baseline ADR.

ADR - adenoma detection rate; BSCP - bowel cancer screening programme; CI – confidence intervals; CIT – caecal intubation time; ITT – intention-to-treat; MAP - mean number of adenomas per patient

Table B4: Summary of methods for randomised controlled trials: E-Cap

Study name (acronym)	E-Cap
Objectives	To investigate the impact of ENDOCUFF VISION®-assisted colonoscopy on polyp detection, as compared to standard colonoscopy, in the UK Bowel Cancer Screening Programme (BCSP)
Location	UK (single centre)
Design	Randomised controlled trial
Duration of study	12 months – Sept 2014 to Sept 2015
Sample size	534
Inclusion criteria	Patients aged 59-75 years referred for BCSP colonoscopy with positive FOBT
Exclusion criteria	Patients with a history of inflammatory bowel disease or polyposis syndromes
Method of randomisation	Participants were randomised using a 1:1 ratio among the two study arms using random permuted blocks of randomly varying sizes. Participants were given a sequential study number and then assigned to the allocated intervention from

Study name (acronym)	E-Cap
	the random list.
Method of blinding	Patients were given a sequential study number and then assigned to the associated intervention from the random list. The generated list was concealed in a sequentially numbered sealed opaque envelopes. The participant but not the endoscopist was blinded to the allocation.
Intervention(s) (n=)	ENDOCUFF VISION® (n = 266)
Comparator(s) (n =)	Standard colonoscopy (n = 265)
Baseline differences	NR
Duration of follow-up, lost to follow-up information	Three patients were subsequently excluded following the unexpected finding of hyperplastic polyposis during colonoscopy.
Statistical tests	Fisher's exact test was used to compare ADR, MAP, PDR and cancer detection rate. Log rank test was used to compare withdrawal times. A chi-squared test was used to compare endoscopist view and comfort scores.
Primary outcomes	Mean number of polyps per patient (MPP) defined as the total number of polyps divided by the total number of patients in that group.
Secondary outcomes	ADR, advanced ADR >10mm in size, MAP, PDR, cancer detection rate, CIT, withdrawal times, comfort scores.

ADR - adenoma detection rate; BSCP - bowel cancer screening programme; CIT – caecal intubation time; MAP - mean number of adenomas per patient**;** MPP – mean number of polyps per patient**;**NR- not reported

Table B5: Summary of methods for observational studies: Tsiamoulos 2018

Study name (acronym)	Tsiamoulos 2018
Objectives	To evaluate the impact of ENDOCUFF VISION® on colonoscopist's performance during screening.
Location	UK (single centre)
Design	Prospective observational study
Duration of study	17 months - April 2013 to Sept 2014
Sample size	410
Inclusion criteria	Patients referred with positive faecal occult blood tests to undergo a screening colonoscopy through the National Health Service (NHS) BCSP. Each colonoscopist was allowed to use the device at their own discretion (nonrandomised study) for a designated "cuff" period.
Exclusion criteria	Non-completed (failure to intubate the caecum) colonoscopies were excluded from the analysis and were considered "failed cases" in all separate time periods.
Intervention(s) (n =)	ENDOCUFF VISION® (n = 136)
Comparator(s) (n =)	Standard colonoscopy (n = 274: pre-cuff = 137, post-cuff = 137)
Baseline differences	NR
How were participants followed-up (for example, through proactive follow-up or passively). Duration of follow-up, participants lost to follow-up.	NR
Statistical tests	T-test two sample assuming equal variances. To allow

Study name (acronym)	Tsiamoulos 2018
	for multiple comparisons among the pairs of time periods, the results from these pairwise comparisons were adjusted using the Bonferroni method. Both p values and CIs for differences between time periods were adjusted. The X^2 and Kruskal-Wallis tests were used to compare among the 3 time periods. Mann-Whitney test was used to compare across pairs of time period 9pre-cuff, cuff and post-cuff).
Primary outcomes	ADR, MAP, CIR, CIT, negative colonoscopy withdrawal time (NCWT), conscious sedation level, comfort. None of the outcomes were reported specifically as primary or secondary.
Secondary outcomes	

ADR - adenoma detection rate; BSCP - bowel cancer screening programme; CI – confidence intervals; CIT – caecal intubation time; MAP - mean number of adenomas per patient; NCWT – negative colonoscopy withdrawal time; NHS – National Health Service; NR- not reported

Table B6: Summary of methods for observational studies: Rameshshanker 2016

Study name (acronym)	Rameshshanker 2016 (Rameshshanker et al. 2016)
Objectives	To assess the SP6 for an individual colonoscopist during standard and Endocuff-assisted colonoscopy. SP6 is a new measure of colonoscopy efficiency that can be used to evaluate both individual endoscopist's performance and to compare different detection interventions.
Location	UK
Design	Prospective service evaluation
Duration of study	11 months - Oct 2014 to Sept 2015
Sample size	96
Inclusion criteria	Screening colonoscopies performed by an experienced endoscopist between October 2014 and September 2015
Exclusion criteria	NR
Intervention(s) (n =)	ENDOCUFF VISION®
Comparator(s) (n =)	Standard colonoscopy
Baseline differences	NR
How were participants followed-up (for example, through proactive follow-up or passively). Duration of follow-up, participants lost to follow-up.	NR
Statistical tests	NR
Primary outcomes	Assess SP6 (adenomas + sessile serrated polyps/adenomas)
Secondary outcomes	CIT, withdrawal time, number of ADR, number of sessile serrated polyps/adenomas

ADR - adenoma detection rate; CIT – caecal intubation time; NR- not reported; SP6 – sessile serrated polyps 6; UK – United Kingdom

7.4.2 Provide details on data from any single study that have been drawn from more than one source (for example a poster and unpublished report) and/or when trials are linked this should be made clear (for example, an open-label extension to randomised controlled trial).

Five publications reported data for the ADENOMA trial; two full-text publications, two abstracts and a clinical trial record. One article, published in 2016, reported protocol information only and the two abstracts reported interim data. All data were extracted from the journal article published in 2018.

Five publications reported data for the E-Cap study; one full-text publication, three occurrences of the same conference abstract (published in three different sources (Bhattacharyya et al. 2016a, Bhattacharyya et al. 2016b, Bhattacharyya et al. 2016c)), and a clinical trial record (Portsmouth Hospitals NHS Trust 2015). Although the majority of data were extracted from the full-text publication, some additional population details were extracted from the clinical trial record.

Eight publications were identified in association with Tsiamoulos 2018; seven abstracts published between 2014 and 2015 reported interim data and one full text publication. Only the full-text publication reported final data for the whole population and was considered for data extraction.

One publication, an abstract published in 2016, was identified for Rameshshanker 2016.

7.4.3 Highlight any differences between patient populations and methodology in all included studies.

Two of the four comparative studies were randomised controlled trials (ADENOMA and E-CAP) and two were observational studies (Tsiamoulos 2018 and Rameshshanker 2016) . All of the studies evaluated ENDOCUFF VISION® compared with standard colonoscopy and were conducted in UK hospital settings. The studies ranged in size from 96 patients (Rameshshanker 2016) to 1772 patients (ADENOMA) . Study duration ranged from 11 months (E-Cap) to 17 months (Tsiamoulos 2018) .

Common outcomes reported across the studies include ADR, MAP, CIT and withdrawal time. The duration of follow up was reported by one study (ADENOMA) at 21 days. ADENOMA reported that no patients were lost to follow up. In the E-Cap study, the authors reported that 3 patients were excluded from the analysis following unexpected findings of hyperplastic polyposis during the colonoscopy.

Two studies reported the eligible age of patients. This was 59 to 75 years in the E-Cap study and 18 years and over in ADENOMA. Three studies (E-Cap, Tsiamoulos 2018 and Rameshshanker 2016) reported the median age of patients, which ranged from 65 to 68 years. The ADENOMA study reported the mean age of patients to be 61.7 and 62.1 years in the ENDOCUFF VISION® and standard colonoscopy arms respectively.

Three studies (E-Cap, ADENOMA and Tsiamoulos 2018) reported details of patient gender, with the proportion of males ranging from 53.3% to 67.9% across arms.

In E-Cap, patients were included for screening and surveillance colonoscopies. Patients in ADENOMA were included for screening, surveillance and diagnostic colonoscopies. Outcome data for the ADENOMA study were reported separately for screening and surveillance and for diagnostic procedures. Two studies (Tsiamoulos 2018 and Rameshshanker 2016) only included patients receiving screening colonoscopies. Specific details on patient indication for colonoscopy were reported by two studies (E-Cap and ADENOMA) and details are reported in Three studies (ADENOMA, Tsiamoulos 2018 and Rameshshanker 2016) reported the number of endoscopists involved, ranging from one (Rameshshanker 2016) to 48 (ADENOMA) . In ADENOMA, all of the colonoscopists had previous experience with ENDOCUFF VISION® and received training. Further, each site was limited to 4 BCSP colonoscopists. The authors reported that this was due to the additional accreditation required for the English BCSP, which may not reflect typical colonoscopy practice. In Tsiamoulos 2018, only one of the four operators had previous experience with ENDOCUFF VISION®. In Rameshshanker 2016, the authors reported that the endoscopists were

experienced, but provided no further details on the extent of that experience. The E-Cap study did not report the number of endoscopists. However, the authors did report that all of the endoscopists were highly experienced with excellent performance indicators including a baseline ADR of 58.9 % in the FOBT-positive screening population before the start of the study, which they stated was a lot higher than the national average ADR (Logan et al. 2012). Further, these reported performance indicators are considerably higher than the minimal standard (15%) and aspirational target (20%) for ADR set by the British Society for Gastroenterology .

Two of the 4 studies (E-Cap and ADENOMA) reported details on the quality of bowel preparation (Bhattacharyya et al. 2017). In the E-Cap study, good / adequate bowel preparation was reported in 97.7% of patients across both arms (Bhattacharyya et al. 2017). In ADENOMA, the authors reported that bowel preparation was of an equivalent standard in both groups. Further, ADENOMA also reported details relating to any requirements to move / manoeuvre patients (Ngu et al. 2018a). Two studies (ADENOMA and Tsiamoulos 2018) reported details of the use of drugs during the procedure. In ADENOMA, a proportion of patients in both arms received hyoscine-n-butylbromide and carbon dioxide gas. In Tsiamoulos 2018, patients received varying doses of midazolam and fentanyl.

Table B7 and Table B9 show the full study characteristics, patient characteristics and details of the procedures.

Table B7: Eligible studies: study characteristics

Study name (acronym)	Study design	Location/ setting	Sample size	Duration of study	Primary outcomes	Secondary outcomes	Duration of follow up	Loss to follow up
ADENOMA	RCT	One academic and six community hospitals, UK	1772	15 months (Nov 2014 to Feb 2016)	Difference in ADR between ENDOCUFF VISION® assisted colonoscopy and standard colonoscopy	MAP, polyp distribution (including assessment of cancer detection), detection of SSP, rate of cuff exchange, CIT, insertion time to caecum, withdrawal time, patient experience, future colonoscopic workload due to increased ADR, difference in ADR between BCSP and non-BCSP colonoscopists, changes in ADR throughout the trial, colonoscopist baseline ADR	21 days	No patients were lost to follow-up
E-Cap	RCT	One Hospital, UK	534	12 months (Sept 2014 to Sept 2015)	MPP	ADR; number of adenomas per patient; advanced ADR > 10mm in size; PDR; MAP cancer detection rate, CIT, withdrawal times, comfort scores	NR	3 patients excluded following hyperplastic polyposis during colonoscopy
Tsiamoulos 2018	Observational	Hospital, UK	410 (137 pre-cuff, 136 cuff, 137 post-cuff	17 months (April 2013 - Sept 2014)	Not specified as primary and secondary: ADR, MAP, CIR, CIT, NCWT, sedation level, comfort score and nursing comfort score		NR	NR

Study name (acronym)	Study design	Location/ setting	Sample size	Duration of study	Primary outcomes	Secondary outcomes	Duration of follow up	Loss to follow up
Rameshshanker 2016	Observational	Hospital, UK	96	11 months (Oct 2014 – Sept 2015)	SP6 (adenomas + SSP/A)	CIT; Withdrawal time; Number of polyps; Number of adenomas; SSP/A; ADR	NR	

ADR - adenoma detection rate; BSCP - bowel cancer screening programme; CIT – caecal intubation time; MAP - mean number of adenomas per patient**;** MPP – mean polyps per person; NR – not reported; NCWT – negative colonoscopy withdrawal time; PDR – polyp detection rate; RCT – randomised controlled trials; SSP/A - sessile serrated polyps/adenomas UK – United Kingdom

Table B8: Eligible studies: Patient characteristics

Study name (acronym)	Type of colonoscopy	Eligible age (years)	Age in years Mean (SD)	Males n (%)	Indication for colonoscopy Number (%)	Population: screening, surveillance or diagnostic
ADENOMA	ENDOCUFF VISION®	≥18	61.7 (11.7)	507 (57.1)	BCSP: 274 (30.9) BCSP surveillance: 89 (10) Colonoscopy conversion from bowel scope: 31 (3.5) Symptomatic diagnostic: 357 (40.2) Symptomatic surveillance: 137 (15.4)	Screening, surveillance, diagnostic
	Standard colonoscopy		62.1 (11.1)	502 (56.8)	BCSP: 282 (32) BCSP surveillance: 88 (10) Colonoscopy conversion from bowel scope: 32 (3.6) Symptomatic diagnostic: 346 (39.1) Symptomatic surveillance: 135 (15.3)	
E-Cap	ENDOCUFF VISION®	60 - 75	Median 68 [IQR 63-70]	162 (60.9)	Positive FOBT: 188 (70.7) Polyp surveillance: 78 (29.3)	Screening and surveillance
	Standard colonoscopy		Median 67 [IQR 64-71]	180 (67.9)	Positive FOBT: 183 (69.1) Polyp surveillance: 82 (30.9)	
Tsiamoulos 2018	ENDOCUFF VISION®	NR	Median 65 [IQR 62-70]	76 (55.9)	NR	Screening
	Standard colonoscopy		Pre-cuff: Median 67 [IQR 63-71] Post-cuff: Median 66 [IQR 61-70]	Pre-cuff: 81 (59.1) Post-cuff: 73 (53.3)		
Rameshshanker 2016	ENDOCUFF VISION®	NR	Median 65 (range 55 – 74)	NR	NR	Screening
	Standard colonoscopy					

BSCP - bowel cancer screening programme; FOBT – faecal occult blood test; IQR – interquartile range; NR – not reported

Table B9: Eligible studies: Details of procedure

Study name (acronym)	Type of colonoscopy	Person performing the endoscopy (number)	Level of experience	Quality of bowel preparation	Requirements to move / manoeuvre patients Number (%)	Use of drugs during procedure
ADENOMA	ENDOCUFF VISION®	Colonoscopists (48) of whom 17 were BCSP colonoscopists)	All colonoscopists were required to perform a minimum of 20 cases with ENDOCUFF VISION® prior to study commencement and were trained by means of a presentation and video	NR Bowel preparation was of an equivalent standard in both groups	Position change: All pts: 718 (81.3) BSCP: 326 (83.2) Non-BSCP: 392 (79.8) Rectal reflexion: All pts: 723 (81.4) BSCP: 322 (81.7) Non-BSCP: 401 (81.2)	Hyoscine-n-butylbromide: All pts: 627 (70.6) BSCP: 300 (76.1) Non-BSCP: 327 (66.2) Carbon dioxide gas: All pts: 672 (75.7) BSCP: 357 (90.6) Non-BSCP: 315 (63.8)
	Standard colonoscopy				Position change: All pts: 772 (87.5) BSCP: 359 (89.3) Non-BSCP: 413 (86.0) Rectal reflexion: All pts: 785 (88.8) BSCP: 363 (90.1) Non-BSCP: 422 (87.7)	Hyoscine-n-butylbromide: All pts: 568 (64.3) BSCP: 309 (76.7) Non-BSCP: 259 (53.9) Carbon dioxide gas: All pts: 678 (76.7) BSCP: 367 (91.1) Non-BSCP: 311 (64.7)
E-Cap	ENDOCUFF VISION®	Endoscopists (NR) Baseline ADR 58.9%)	Accredited BCSP endoscopists, who had carried out >5000 colonoscopies and had caecal intubation rates of >90%	NR	NR	NR
	Standard colonoscopy					
Tsiamoulos 2018	ENDOCUFF VISION®	Endoscopists (4)	One of the four operators had previous experience with ENDOCUFF VISION®	NR	NR	Midazolam: mean 0.86mg Fentanyl: mean 33mcg
	Standard colonoscopy					Midazolam: Pre-cuff: mean 1.03 mg; Post-cuff: 0.99mg

Study name (acronym)	Type of colonoscopy	Person performing the endoscopy (number)	Level of experience	Quality of bowel preparation	Requirements to move / manoeuvre patients Number (%)	Use of drugs during procedure
						Fentanyl: Pre-cuff: mean 34mcg; Post-cuff: mean 36mcg
Rameshshanker 2016	ENDOCUFF VISION® Standard colonoscopy	Endoscopist (1)	"experienced"	NR	NR	NR

ADR - adenoma detection rate; BSCP - bowel cancer screening programme; NR – not reported

7.4.4 Provide details of any subgroup analyses that were undertaken in the studies included in Section 7.4.1. Specify the rationale and state whether these analyses were pre-planned or post-hoc.

In the ADENOMA study, outcome data are reported separately for the subgroups of patients who were referred to colonoscopy through the BCSP and those who were not referred through the BCSP.

7.4.5 If applicable, provide details of the numbers of patients who were eligible to enter the study(s), randomised, and allocated to each treatment in an appropriate format.

Details of the number of patients eligible, randomised and allocated to each arm were reported in the two RCTs and the patient flow diagrams are presented in Figure B2 and Figure B3.

Figure B2: Participant flow in the ADENOMA trial (Ngu et al. 2018a)

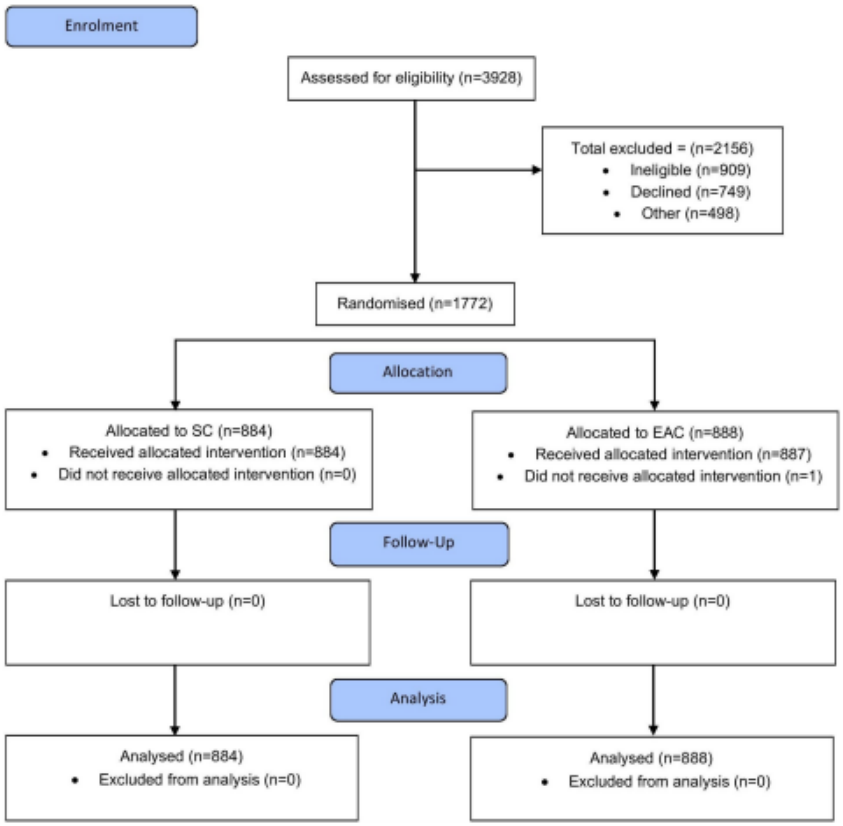
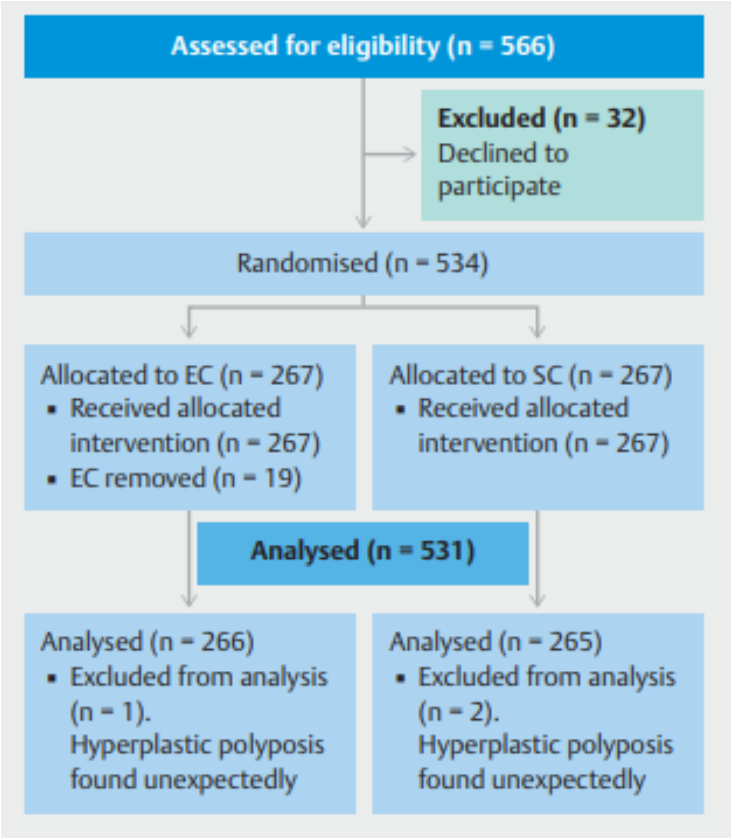


Figure B3: Participant flow in E-CAP (Bhattacharyya et al. 2017)



7.4.6 If applicable provide details of and the rationale for, patients that were lost to follow-up or withdrew from the studies.

One study (ADENOMA) specifically reported that no patients were lost to follow-up at the 21-day follow up. In E-Cap, three patients were excluded from analysis following the unexpected finding of hyperplastic polyposis during colonoscopy. The other two studies did not report details of follow up.

7.5 Critical Appraisal of Relevant Studies

7.5.1 Complete a separate quality assessment table for each study.

Critical appraisals for each eligible study are presented in Table B10 to B13 below. Three studies were assessed to have an unclear risk of bias due to limited reporting of key criteria. The ADENOMA study was considered to have a low risk of bias.

Table B10: Critical appraisal of randomised control trials: ADENOMA

Study name (acronym)	ADENOMA	
Study question	**Response: (yes/no/not clear/N/A)**	**How is the question addressed in the study**
Was randomisation carried out appropriately?	Yes	Stratified randomisation based on age, gender, hospital site and BCSP status was performed using a dynamic adaptive algorithm created by the North Wales Organisation for Randomised Trials in Health Clinical Trials Unit. Randomisation was via a computerised internet based platform.
Was the concealment of treatment allocation adequate?	No	Patients, colonoscopists and research nurses were not blinded to allocation.
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	Patient characteristics were comparable in both groups.
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	No	Patients, colonoscopists and research nurses were not blinded to randomisation arm, but all study analyses were conducted in a blinded fashion
Were there any unexpected imbalances in dropouts between groups? If so, were they explained or adjusted for?	No	One patient, allocated to ENDOCUFF VISION did not receive the intervention. No patients were lost to follow up.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	Results were reported for all pre-specified outcomes
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	All superiority analyses were performed on an intention-to-treat (ITT) basis. No patients were lost to follow up.
Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

ITT – intention to treat

Table B11: Critical appraisal of randomised control trials: E-Cap

Study name (acronym)	E-Cap	
Study question	**Response: (yes/no/not clear/N/A)**	**How is the question addressed in the study**
Was randomisation carried out appropriately?	Yes	Randomization was performed in a 1:1 ratio among the two study arms using random permuted blocks of randomly varying sizes.
Was the concealment of treatment allocation adequate?	Yes	The successive participants were given a sequential study number and then assigned to the associated intervention from the random list. The generated list was concealed in sequentially numbered sealed opaque envelopes, which were only opened to reveal the allocation after verifying that the participant was eligible and had consented to enter the trial.
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Not clear	Patients were matched on age, proportion of males and indication. Other characteristics not reported.
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Not clear	Insufficient information was provided to permit judgement. The clinical trial record (NCT02529007) states that the study masking was “Single blind (subject)”, but this is not described in sufficient detail.
Were there any unexpected imbalances in dropouts between groups? If so, were they explained or adjusted for?	No	3 patients were excluded (due to new diagnosis of polyposis syndrome) but this reportedly occurred before randomisation.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	Results were reported for all pre-specified outcomes
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	ITT analysis was conducted in all eligible patients randomised.
Adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD’s guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

ITT – intention to treat

Table B12: Critical appraisal of observational studies: Tsiamoulos 2018

Study name (acronym)	Tsiamoulos 2018	
Study question	**Response: (yes/no/not clear/N/A)**	**How is the question addressed in the study**
Was the cohort recruited in an acceptable way?	Yes	All patients referred with positive faecal occult blood tests to undergo a screening colonoscopy through the National Health Service BCSP were enrolled
Was the exposure accurately measured to minimise bias?	Not clear	Insufficient information was provided to permit judgement
Have the authors identified all important confounding factors?	Not clear	Outcomes included ADR, MAP and CIT which are all subjective outcomes. Furthermore, the endoscopists were not blinded. The authors did not report whether any measures were taken to minimise bias. The authors reported that the device was used at the discretion of the endoscopist.
Have the authors taken into account the confounding factors in the design and/or analysis?	No	Results were not considered in the context of adequacy of bowel cleansing
Was the follow-up of patients complete?	Yes	Insufficient information was provided to permit judgement
How precise (for example, in terms of confidence intervals and p values) are the results?	Not clear	p-values reported but no standard deviations or confidence intervals. Insufficient information was provided to permit judgement
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study		

ADR - adenoma detection rate; BSCP - bowel cancer screening programme; CIT – caecal intubation time; MAP - mean number of adenomas per patient

Table B13: Critical appraisal of observational studies: Rameshshanker 2016

Study name (acronym)	Rameshshanker 2016 (Rameshshanker et al. 2016)	
Study question	**Response: (yes/no/not clear/N/A)**	**How is the question addressed in the study**
Was the cohort recruited in an acceptable way?	Not clear	Insufficient information was provided to permit judgement
Was the exposure accurately measured to minimise bias?	Not clear	Insufficient information was provided to permit judgement
Have the authors identified all important confounding factors?	Not clear	Insufficient information was provided to permit judgement
Have the authors taken into account the confounding factors in the design and/or analysis?	Not clear	Insufficient information was provided to permit judgement
Was the follow-up of patients complete?	Not clear	Insufficient information was provided to permit judgement
How precise (for example, in terms of confidence intervals and p values) are the results?	Not clear	Insufficient information was provided to permit judgement
Adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence 12 questions to help you make sense of a cohort study		

7.6 Results of the Relevant Studies

7.6.1 Complete a results table for each study with all relevant outcome measures pertinent to the decision problem.

The results of each of the included studies are presented in the tables below.

For the ADENOMA trial, the results for detection rate, mean number of growths detected per procedure, caecal intubation and withdrawal times, caecal intubation rate and quality of colonoscopy are presented in Table B14 to Table B18.

For the E-Cap trial, results are presented for the detection rate, mean number of growths detected per procedure and quality of colonoscopy in Table B19 to Table B22.

For the Tsiamoulos 2018 study, results for the detection rate, mean number of growths detected per procedure and caecal intubation and withdrawal time

are summarised in Table B23 to Table B25. For the Rameshshanker 2016 study, results for the same outcomes are also presented across Table B26 to Table B28.

Data in italics have been calculated based on other data reported in the study.

Table B14: ADENOMA study: Detection rate

Type of growth	Population	Type of colonoscopy	Location in colon	Number analysed	Patients with ≥1 detection	Detection rate (%)	Difference between ENDOCUFF VISION® vs. Standard colonoscopy (% difference)	p value	Statistical test
Adenoma	Screening, surveillance, diagnostic (all patients)	ENDOCUFF VISION®	All	888	363	40.9	4.7% (95% CI: 0.9 to ∞)	0.02	One sided chi-squared test
		Standard		884	320	36.2			
	Screening, surveillance (BSCP)	ENDOCUFF VISION®	All	394	243*	61.7	10.8% (95% CI: 5.1 to ∞)	0.001	One sided chi-squared test
		Standard		403	205*	50.9			
	Symptomatic diagnostic / surveillance (non-BSCP)	ENDOCUFF VISION®	All	494	120	24.3	0.4% (95% CI: -4.1 to ∞)	0.44	One sided chi-squared test
		Standard		481	115	23.9			
	Screening, surveillance, diagnostic (all patients)	ENDOCUFF VISION®	Left colon	888	232	26.1	4% (97.5% CI: 0.6 to ∞)	0.03	One sided chi-squared test
		Standard		884	196	22.2			
	Screening, surveillance (BSCP)	ENDOCUFF VISION®		394	161	40.9	8.1% (97.5% CI: 2.5 to ∞)	0.009	One sided chi-squared test
		Standard		403	132	32.8			
	Symptomatic diagnostic / surveillance (non-BSCP)	ENDOCUFF VISION®		494	71	14.4	1.1% (97.5% CI: -2.6 to ∞)	0.31	One sided chi-squared test
		Standard		481	64	13.3			
	Screening, surveillance, diagnostic (all patients)	ENDOCUFF VISION®	Right colon	888	244	27.5	2.7% (97.5% CI: -0.7 to ∞)	0.1	One sided chi-squared test
		Standard		884	219	24.8			
	Screening, surveillance (BSCP)	ENDOCUFF VISION®		394	170	43.2	5.2% (97.5% CI: -0.5 to ∞)	0.07	One sided chi-squared test
		Standard		403	153	38			
		ENDOCUFF VISION®		494	74	15	1.3% (97.5% CI: -2.4 to ∞)	0.29	

Type of growth	Population	Type of colonoscopy	Location in colon	Number analysed	Patients with ≥1 detection	Detection rate (%)	Difference between ENDOCUFF VISION® vs. Standard colonoscopy (% difference)	p value	Statistical test
	Symptomatic diagnostic / surveillance (non-BSCP)	Standard		481	66	13.7			One sided chi-squared test
Adenoma (10+mm)	Screening, surveillance, diagnostic (all patients)	ENDOCUFF VISION®	NR	888	70	7.9	1% (97.5% CI: -1.1 to ∞)	0.21	One sided chi-squared test
		Standard		884	61	6.9			
	Screening, surveillance (BSCP)	ENDOCUFF VISION®	NR	394	54	13.7	1.3% (97.5% CI: -2.6 to ∞)	0.29	One sided chi-squared test
		Standard		403	50	12.4			
	Symptomatic diagnostic / surveillance (non-BSCP)	ENDOCUFF VISION®	NR	494	16	3.2	1.0% (97.5% CI: -0.8 to ∞)	0.18	One sided chi-squared test
		Standard		481	11	2.3			
Adenoma (6-9mm)	Screening, surveillance, diagnostic (all patients)	ENDOCUFF VISION®	NR	888	94	10.6	2.9% (97.5% CI: 0.6 to ∞)	0.02	One sided chi-squared test
		Standard		884	68	7.7			
	Screening, surveillance (BSCP)	ENDOCUFF VISION®	NR	394	75	19	5.4% (97.5% CI: 4.2 to ∞)	<0.001	One sided chi-squared test
		Standard		403	43	10.7			
	Symptomatic diagnostic / surveillance (non-BSCP)	ENDOCUFF VISION®	NR	494	19	3.9	-1.4% (97.5% CI: -3.5 to ∞)	0.85	One sided chi-squared test
		Standard		481	25	5.2			
Adenoma (<5mm)	Screening, surveillance, diagnostic (all patients)	ENDOCUFF VISION®	NR	888	307	34.6	3.8% (97.5% CI: 0.1 to ∞)	0.04	One sided chi-squared test
		Standard		884	272	30.8			
	Screening, surveillance (BSCP)	ENDOCUFF VISION®	NR	394	205	52	7.4% (97.5% CI: 1.6 to ∞)	0.02	One sided chi-squared test
		Standard		403	180	44.7			
		ENDOCUFF VISION®	NR	494	102	20.7	1.5% (97.5% CI: -2.7 to ∞)	0.28	

Type of growth	Population	Type of colonoscopy	Location in colon	Number analysed	Patients with ≥1 detection	Detection rate (%)	Difference between ENDOCUFF VISION® vs. Standard colonoscopy (% difference)	p value	Statistical test
	Symptomatic diagnostic / surveillance (non-BSCP)	Standard		481	92	19.1			One sided chi-squared test
Polyp	Screening, surveillance, diagnostic (all patients)	ENDOCUFF VISION®	NR	888	480	54.1	6.1% (97.5% CI: 2.2 to ∞)	0.005	One sided chi-squared test
		Standard		884	424	48			
	Screening, surveillance (BSCP)	ENDOCUFF VISION®	NR	394	291	73.9	10.6% (97.5% CI: 5.2 to ∞)	<0.001	One sided chi-squared test
		Standard		403	255	63.3			
	Symptomatic diagnostic / surveillance (non-BSCP)	ENDOCUFF VISION®	NR	494	189	38.3	3.1% (97.5% CI: -2.0 to ∞)	0.16	One sided chi-squared test
		Standard		481	169	35.1			
Sessile serrated adenomas	Screening, surveillance, diagnostic (all patients)	ENDOCUFF VISION®	NR	888	20	2.3	1.1% (97.5% CI: 0.1 to ∞)	0.03	One sided chi-squared test
		Standard		884	10	1.1			
	Screening, surveillance (BSCP)	ENDOCUFF VISION®	NR	394	8	2	0.8% (97.5% CI: -0.7 to ∞)	0.19	One sided chi-squared test
		Standard		403	5	1.2			
	Symptomatic diagnostic / surveillance (non-BSCP)	ENDOCUFF VISION®	NR	494	12	2.4	1.4% (97.5% CI: 0.0 to ∞)	0.05	One sided chi-squared test
		Standard		481	5	1			
Cancer	Screening, surveillance, diagnostic (all patients)	ENDOCUFF VISION®	NR	888	36	4.1	1.8% (95% CI: 0.4 to ∞)	0.02	One sided chi-squared test
		Standard		884	20	2.3			
	Screening, surveillance (BSCP)	ENDOCUFF VISION®	NR	394	26	6.6	2.9% (95% CI: 0.3 to ∞)	0.03	One sided chi-squared test
		Standard		403	15	3.7			
		ENDOCUFF VISION®	NR	494	10	2	1% (95% CI: -0.3 to ∞)	0.11	

Type of growth	Population	Type of colonoscopy	Location in colon	Number analysed	Patients with ≥1 detection	Detection rate (%)	Difference between ENDOCUFF VISION® vs. Standard colonoscopy (% difference)	p value	Statistical test
	Symptomatic diagnostic / surveillance (non-BSCP)	Standard		481	5	1			One sided chi-squared test

BSCP - bowel cancer screening programme; CI – confidence intervals; NR not reported; * - self-calculated using other available data.

Table B15: ADENOMA: Mean number of growths detected per procedure

Type of growth	Population	Type of colonoscopy	Location in colon	Number analysed	Mean number per procedure	Standard deviation	Difference between ENDOCUFF VISION® vs. Standard colonoscopy	p value	Statistical test
Adenoma	Screening, surveillance, diagnostic (all patients)	ENDOCUFF VISION®	All	888	0.95	1.89	0.2 (97.5% CI: 0.07 to ∞)	0.02	One sided chi-squared test
		Standard		884	0.75	1.4			
	Screening, surveillance (BSCP)	ENDOCUFF VISION®	All	394	1.59	2.32	0.39 (97.5% CI: 0.15 to ∞)	0.004	One sided chi-squared test
		Standard		403	1.2	1.77			
	Symptomatic diagnostic / surveillance (non-BSCP)	ENDOCUFF VISION®	All	494	0.44	1.24	0.07 (97.5% CI: -0.04 to ∞)	0.42	One sided chi-squared test
		Standard		481	0.37	0.8			

BSCP - bowel cancer screening programme; CI – confidence intervals.

Table B16: ADENOMA: Insertion time and withdrawal time

Population	Type of colonoscopy	Number analysed	Median (minutes)	Interquartile range (minutes)	Difference between ENDOCUFF VISION® vs. Standard colonoscopy	p value	Statistical test
Caecal intubation time							
Screening, surveillance, diagnostic (all patients)	ENDOCUFF VISION®	888	8	5-12	-1 minute (97.5% CI: -∞ to 0)	0.001	Non-inferiority margin: 1 minute
	Standard	884	9	6-15			
Screening, surveillance (BSCP)	ENDOCUFF VISION®	394	7	4-10	0 minute (97.5% CI: -∞ to 1)	NR	Non-inferiority margin: 1 minute
	Standard	403	6	4-11			
Symptomatic diagnostic / surveillance (non-BSCP)	ENDOCUFF VISION®	494	10	7-14	-2 minute (97.5% CI: -∞ to -1)	NR	Non-inferiority margin: 1 minute
	Standard	481	12	8-17			
Withdrawal time							
Screening, surveillance, diagnostic (all patients)	ENDOCUFF VISION®	NR – patients where no polyps were found	8	6-10	0 minute (97.5% CI: -∞ to 0)	NR	Non-inferiority margin: 1 min
	Standard		8	6-11			
Screening, surveillance (BSCP)	ENDOCUFF VISION®		8	6-10	-1 minute (97.5% CI: -∞ to 0)	NR	Non-inferiority margin: 1 min
	Standard		9	7-12			
Symptomatic diagnostic / surveillance (non-BSCP)	ENDOCUFF VISION®		7	5-10	0 minute (97.5% CI: -∞ to 1)	NR	Non-inferiority margin: 1 min
	Standard		7	5-10			

BSCP - bowel cancer screening programme; CI – confidence intervals; NR not reported.

Table B17: ADENOMA: Caecal intubation rate

Population (screening, surveillance or diagnostic)	Type of colonoscopy	Number analysed	Number of events	%	Difference between ENDOCUFF VISION® vs. Standard colonoscopy	P value	Statistical test
Screening, surveillance, diagnostic (all patients)	ENDOCUFF VISION®	888	858	96.7	0.4% (97.5% CI: -1.3 to ∞)	NR	Non-inferiority margin: 5%
	Standard	884	852	96.4			
Screening, surveillance (BSCP)	ENDOCUFF VISION®	394	384	97.7	-0.1% (97.5% CI: -2.1 to ∞)	NR	Non-inferiority margin: 5%
	Standard	403	394	97.8			
Symptomatic diagnostic / surveillance (non-BSCP)	ENDOCUFF VISION®	494	474	96	0.7% (97.5% CI: -1.8 to ∞)	NR	Non-inferiority margin: 5%
	Standard	481	458	95.2			

BSCP - bowel cancer screening programme; CI – confidence intervals; NR not reported.

Table B18: ADENOMA: Quality of colonoscopy

PRO measure	Type of colonoscopy	Number analysed	Mean	Standard Deviation	Difference between ENDOCUFF VISION® vs. Standard colonoscopy	P value	Statistical test
Patients were asked specifically about discomfort on anal intubation	ENDOCUFF VISION®	NR	NR	NR	8.6% of patients found anal discomfort more uncomfortable with ENDOCUFF-VISION® (23.6% vs 15%); for all other measures of comfort ENDOCUFF-VISION® was non-inferior to standard colonoscopy	NR	NR
	Standard	NR	NR	NR			

NR- not reported.

Table B19: E-Cap (Bhattacharyya et al. 2016a, Bhattacharyya et al. 2016b, Bhattacharyya et al. 2016c, Portsmouth Hospitals NHS Trust 2015, Bhattacharyya et al. 2017): Detection rate

Type of growth	Type of colonoscopy	Location in colon	Number analysed	Patients with ≥1 detection	Detection rate (%)	Difference between ENDOCUFF VISION® vs. Standard colonoscopy	p value	Statistical test
Polyps	ENDOCUFF VISION®	NR	266	187	70.3	*Increased detection rate by 0.5%*	0.93	Fisher's exact test
	Standard		265	185	69.8			
Adenoma	ENDOCUFF VISION®	NR	266	162	60.9	*Decreased detection rate by 2.1%*	0.85	Fisher's exact test
	Standard		265	167	63			
Adenoma (>10mm)	ENDOCUFF VISION®	NR	266	45*	16.9	*Decreased detection rate by 1.6%*	0.81	Fisher's exact test
	Standard		265	49*	18.5			
Cancer	ENDOCUFF VISION®	NR	266	14	5.3	*Decreased detection rate by 0.4%*	0.85	Fisher's exact test
	Standard		265	15	5.7			

Data in italics have been calculated. NR – not reported. * – self-calculated using other available data.

Table B20: E-Cap (Bhattacharyya et al. 2016a, Bhattacharyya et al. 2016b, Bhattacharyya et al. 2016c, Portsmouth Hospitals NHS Trust 2015): Mean number of growths detected per procedure

Type of growth	Type of colonoscopy	Location in colon	Number analysed	Number detected	Mean number detected per procedure	Standard deviation	Difference between ENDOCUFF VISION® vs. Standard colonoscopy	p value	Statistical test
Polyps	ENDOCUFF VISION®	NR	266	436	1.6	1.9	*Decrease of 0.14 MPP*	0.44	Fisher's exact test
	Standard		265	470	1.8	2			
Adenoma	ENDOCUFF VISION®	NR	266	336	1.3	1.8	*Decrease 0.1 MAP*	0.54	Fisher's exact test
	Standard		265	359	1.4	1.5			

Data in italics have been calculated. MAP - mean number of adenomas per patient; NR- not reported.

Table B21: E-Cap (Bhattacharyya et al. 2016a, Bhattacharyya et al. 2016b, Bhattacharyya et al. 2016c, Portsmouth Hospitals NHS Trust 2015): Duration of colonoscopy, caecal intubation time and withdrawal time

Type of colonoscopy	Number analysed	Mean	Standard deviation	Difference between ENDOCUFF VISION® vs. Standard colonoscopy	p value	Statistical test
Duration of colonoscopy						
ENDOCUFF VISION®	266	32.8	NR	*Decrease in mean time of 2.48 minutes*	0.11	Log rank test
Standard	265	35.28				
Caecal intubation time						
ENDOCUFF VISION®	266	15.75	NR	*Decrease in mean time of 0.14 minutes*	0.86	Log rank test
Standard	265	15.89				
Withdrawal time						
ENDOCUFF VISION®	266	16.9	8.3	*Decrease in mean time of 2.6 minutes*	<0.005	Log rank test
Standard	265	19.5	12.2			

Data in italics have been calculated. NR – not reported.

Table B22: E-Cap (Bhattacharyya et al. 2016a, Bhattacharyya et al. 2016b, Bhattacharyya et al. 2016c, Portsmouth Hospitals NHS Trust 2015): Quality of Colonoscopy

PRO measure	Type of colonoscopy	Number analysed	Mean Comfort score	Standard Deviation	Difference between ENDOCUFF VISION® vs. Standard colonoscopy	P value	Statistical test
Comfort score: 5-point scale, with no discomfort being scored as 0 and severe discomfort scored as 4	ENDOCUFF VISION®	266	1.57	NR	NR	0.27	Chi-squared test
	Standard	265	1.46				

NR- not reported.

Table B23: Tsiamoulos 2018: Detection rate

Type of growth	Type of colonoscopy	Location in colon	Number analysed	Patients with ≥1 detection	Detection rate (%)	Difference between ENDOCUFF VISION® vs. Standard colonoscopy	p value	Statistical test
Adenoma	ENDOCUFF VISION®	NR	136	NR	68.12	Increased ADR of 16% in the during-cuff period compared to pre-cuff period. During the post-cuff period, the detection performance of the three endoscopists declined while maintaining a high detection rate	<0.03 (pre-cuff vs during-cuff)	Bonferroni correction analysis.
	Standard colonoscopy (pre-cuff)		137		52			
	Standard colonoscopy (post-cuff)	NR	137	NR	61.13			

ADR - adenoma detection rate; NR- not reported.

Table B24: Tsiamoulos 2018: Mean number of growths detected per procedure

Type of growth	Type of colonoscopy	Location in colon	Number analysed	Number detected	Mean number of detections per procedure	Difference between ENDOCUFF VISION® vs. Standard colonoscopy	p value	Statistical test
Adenoma	ENDOCUFF VISION®	NR	136	NR	2.2	Increased MAP of 83% in the during-cuff period compared to pre-cuff period. During the post-cuff, 3 endoscopists returned almost to the baseline MAP pre-cuff level	<0.007 (pre-cuff vs during-cuff)	Bonferroni correction analysis.
	Standard colonoscopy (pre-cuff)		137		1.2			
	Standard colonoscopy (post-cuff)	NR	137	NR	1.5			

MAP - mean number of adenomas per patient; NR- not reported.

Table B25: Tsiamoulos 2018: Caecal intubation time and withdrawal time

Type of colonoscopy	Number analysed	Mean time (minutes)	Standard deviation (minutes)	Difference between ENDOCUFF VISION® vs standard colonoscopy	p value	Statistical test
Caecal intubation time						
ENDOCUFF VISION®	136	7	NR	Reduction of 12.5% from pre-cuff to cuff period. Increase of 28.6% from cuff period to post-cuff period	0.002 (pre-cuff vs. cuff) 0.002 (cuff vs. post-cuff)	Mann-Whitney test
Standard colonoscopy (pre-cuff)	137	8	NR			
Standard colonoscopy (post-cuff)	137	9	NR			
Withdrawal time						
ENDOCUFF VISION®	136	8.5	NR	*Decrease in mean withdrawal time of 3.5 minutes compared with pre-cuff and 1.25 minutes compared with post-cuff.*	<0.001 (pre-cuff vs cuff) 0.05 (cuff vs post-cuff)	Mann-Whitney test
Standard colonoscopy (pre-cuff)	137	12	NR			
Standard colonoscopy (post-cuff)	137	9.75	NR			

Data in italics have been calculated. NR- not reported.

Table B26: Rameshshanker 2016 (Rameshshanker et al. 2016): Detection rate

Type of growth	Type of colonoscopy	Location in colon	Number analysed	Patients with ≥1 detection	Detection rate (%)	Difference between ENDOCUFF VISION® vs. Standard colonoscopy	p value	Statistical test
Adenoma	ENDOCUFF VISION®	NR	49	NR	83.67	*Increased detection rate of 28.35%*	0.004	NR
	Standard colonoscopy		47		55.32			

Data in italics have been calculated. NR – not reported.

Table B27: Rameshshanker 2016 (Rameshshanker et al. 2016): Mean number of growths detected per procedure

Type of growth	Type of colonoscopy	Location in colon	Number analysed	Number of growths detected	Mean number of growths per procedure	Difference between ENDOCUFF VISION® vs. Standard colonoscopy	p value	Statistical test
Polyps	ENDOCUFF VISION®	NR	49	113	*2.31*	*Increase in mean number of growths per procedure by 0.99*	<0.001	NR
	Standard		47	62	*1.32*			
Adenoma	ENDOCUFF VISION®	NR	49	95	*1.94*	*Increase in mean number of growths per procedure by 0.85*	0.0005	NR
	Standard		47	51	*1.09*			
Sessile serrated polyps / adenomas (SSP/A)	ENDOCUFF VISION®	NR	49	4	*0.08*	*Increase in mean number of growths per procedure by 0.04*	1	NR
	Standard		47	2	*0.04*			
SP6 (adenomas + SSP/A)	ENDOCUFF VISION®	NR	49	NR	1.11	*Increase in mean number of lesions detected and removed per 6 min withdrawal time 0.51*	0.0004	NR
	Standard		47	NR	0.6			

Data in italics have been calculated. NR – not reported.

Table B28: Rameshshanker 2016 (Rameshshanker et al. 2016): Caecal intubation time and withdrawal time

Type of colonoscopy	Number analysed	Mean time (mins)	Standard deviation (mins)	Difference between ENDOCUFF VISION® vs. Standard colonoscopy	p value	Statistical test
Caecal intubation time						
ENDOCUFF VISION®	49	5.6	3	*Decreased mean caecal intubation time by 0.6 minutes*	NR	NR
Standard	47	6.2	3.85			
Withdrawal time						
ENDOCUFF VISION®	49	10.9	4.5	*Decreased mean withdrawal time by 0.4 minutes*	0.72	NR
Standard	47	11.3	5.33			

Data in italics have been calculated. NR- not reported.

7.6.2 Justify the inclusion of outcomes in table B9 from any analyses other than intention-to-treat.

In Tsiamoulos 2018, only the withdrawal time for negative colonoscopies was reported and, therefore, considered. Withdrawal times for the whole population were not reported by the study authors.

7.7 Adverse Events

In Section 7.7 the sponsor is required to provide information on the adverse events experienced with the technology being evaluated in relation to the scope.

For example, post-marketing surveillance data may demonstrate that the technology shows a relative lack of adverse events commonly associated with the comparator.

7.7.1 Using the previous instructions in sections 7.1 to 7.6, provide details of the identification of studies on adverse events, study selection, study methodologies, critical appraisal and results.

The search approach and strategies described in Section 7.1 was designed to retrieve all studies irrespective of study design relating to the technology and comparators i.e. methodological filters were not applied to the searches. It was envisaged that the strategies developed in Section 7.1 would retrieve all the studies reporting adverse events relating to ENDOCUFF VISION®.

The identified trials reported very limited data in relation to the safety or complications of the devices. All reported complications are presented in Table B29.

7.7.2 Provide details of all important adverse events reported for each study.

Table B29: Eligible studies: Adverse events

Study name (acronym)	Type of colonoscopy	Type of AE or complication	Number analysed	Number of events	%	Additional details
E-Cap	ENDOCUFF VISION®	NR	NR	NR	NR	Postpolypectomy bleeding occurred in one patient in the standard arm. The bleed was identified immediately and was controlled with the application of clips.
	Standard					
ADENOMA	ENDOCUFF VISION®	NR	888	11	NR	No AEs were judged to be related to the use of ENDOCUFF VISION®. Device removal rate was 4.1%, with the most common reason being angulation in a fixed sigmoid colon (52.8%).
	Standard		884	12*		
Tsiamoulos 2018	ENDOCUFF VISION®	Anal discomfort	136	2	1.5	No adverse events were reported from the use of ENDOCUFF VISION®, although it was electively removed in 6 patients where severe sigmoid colon diverticulosis was detected and 2 patients because of discomfort during anal insertion.
	Standard colonoscopy (pre-cuff)	NR	NR	NR	NR	
	Standard colonoscopy (post-cuff)					
Rameshshanker 2016 (Rameshshanker et al. 2016)	ENDOCUFF VISION®	NR	NR	NR	NR	-
	Standard					

NR- not reported; * – self-calculated using other available data.

7.7.3 Describe all adverse events and outcomes associated with the technology in national regulatory databases such as those maintained by the MHRA and FDA (Maude).

Searches were undertaken in national databases for records reporting or suggesting adverse events related to ENDOCUFF VISION®. No relevant records were retrieved from the Medicines and Healthcare products Regulatory Agency (MHRA) web-page [https://www.gov.uk/drug-device-alerts, search date 20 March 2018].

No records were obtained from the U.S Food and Drug Administration (FDA) Manufacturer and User Facility Device (MAUDE) database [https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/search.cfm, search date: 20 March 2018].

7.7.4 Provide a brief overview of the safety of the technology in relation to the scope.

The ADENOMA study design included safety analysis. At study completion this safety analysis did not identify any device related adverse events. Two studies (E-Cap and Rameshshanker 2016) did not report any clear details on adverse events. Some adverse events were reported in Tsiamoulos 2018, however, the authors stated that they were not related to the device. ENDOCUFF VISION® was associated with a slight increase in anal discomfort in the ADENOMA study relative to standard colonoscopy, with the authors stating that these could be minimized in practice.

7.8 Evidence Synthesis and Meta-Analysis

When more than one study is available and the methodology is comparable, a meta-analysis should be considered.

Section 7.8 should be read in conjunction with the 'Medical Technologies Evaluation Programme Methods Guide', available from www.nice.org.uk/mt

7.8.1 Describe the technique used for evidence synthesis and/or meta-analysis. Include a rationale for the studies selected, details of the methodology used and the results of the analysis.

Meta-analysis was not conducted.

7.8.2 If evidence synthesis is not considered appropriate, give a rationale and provide a qualitative review. The review should summarise the overall results of the individual studies with reference to their critical appraisal.

The studies identified were not considered suitable for statistical pooling due to the following issues described below.

In the E-Cap study, the authors reported an unusually high ADR among the endoscopists in the trial, with a baseline rate of 58.9% in the FOBT-positive screening population before the start of the trial and demonstrating any increase on this would be difficult (Bhattacharyya et al. 2017). This was also reflected in the high detection rate in the standard colonoscopy arm of the trial. These detection rates were not considered to represent general clinical practice within the UK, where the average BCSP ADR reported by Lee et al was equal to 46.5%, (Lee et al. 2011), and may have been influenced by participation in a clinical trial. Due to this high baseline, the E-Cap trial showed no significant difference in ADR, polyp detection or cancer detection between ENDOCUFF VISION® and standard colonoscopy amongst bowel cancer screening patients. The withdrawal times, however, were significantly reduced amongst patients who received an ENDOCUFF VISION® assisted colonoscopy. The authors reported that this finding might be due to improved views and stability provided by the device. No significant adverse events were identified.

In the ADENOMA trial, the detection rates for standard colonoscopy were more reflective of rates seen in UK clinical practice. The ADENOMA trial demonstrated that ENDOCUFF VISION® significantly improved ADR (increased detection rate by 4.7%, 95% CI: 0.9 to ∞, p = 0.02), PDR (increased detection by 6.1%, 97.5% CI: 2.2 to ∞, p = 0.005), MAP (increased

detection of 0.2 growths per procedure, 97.5% CI: 0.07 to ∞, p = 0.02) and cancer detection (increased detection rate by 1.8%, 95% CI: 0.4 to ∞, p = 0.02) compared with standard colonoscopy across the ITT population (Ngu et al. 2018a). When considering the screening and surveillance population only (BCSP patients) there was a 10.8% (95% CI: 5.1 to ∞, p = 0.001) and 10.6% (97.5% CI: 5.2 to ∞, p <0.001) increase in ADR and PDR respectively (Ngu et al. 2018a).

Across all of the studies, caecal intubation time was, overall, shorter for ENDOCUFF VISION® patients. In one study (ADENOMA), the difference in caecal intubation time was statistically significant (97.5% CI: ∞ to 0, p = 0.001) and the caecal intubation rate was equivalent in both arms (see Table B17) (Ngu et al. 2018a). It was judged by the authors of the study that no significant adverse events occurred in relation to the use of ENDOCUFF VISION®. However, the authors did report that although ENDOCUFF VISION® was generally well tolerated, it did cause a minor increase in discomfort on anal intubation in patients undergoing colonoscopy with no or minimal sedation.

In Tsiamoulos 2018, the results showed statistically significant increases in ADR (increased detection rate by 16%) and MAP (increased MAP of 83%) amongst BCSP patients when using ENDOCUFF VISION® compared with the 'pre-cuff' period (i.e. standard colonoscopy) (Tsiamoulos et al. 2018). In the 'post-cuff' period (standard colonoscopy), rates of detection declined but remained higher than the 'pre-cuff' period (Tsiamoulos et al. 2018). A reduction in mean caecal intubation and withdrawal times were observed amongst patients who received an ENDOCUFF VISION® assisted colonoscopy (Tsiamoulos et al. 2018). Two cases of anal discomfort were reported amongst patients who received ENDOCUFF VISION®. No other adverse events were reported (Tsiamoulos et al. 2018).

In the Rameshshanker 2016 study, the results showed an increase in ADR (increased detection rate by 28.35%) and MAP (increased detection of 0.85) amongst bowel cancer screening patients receiving ENDOCUFF VISION® assisted colonoscopies compared with standard colonoscopies (Rameshshanker et al. 2016). Increases in the detection of polyps, sessile

serrated polyps/adenomas (SSP/A) and SP6 (adenomas and SSP/A) were also observed amongst ENDOCUFF VISION® patients (Rameshshanker et al. 2016). The findings also demonstrated reductions in caecal intubation and withdrawal times amongst ENDOCUFF VISION® patients (Rameshshanker et al. 2016). No details of adverse events were reported (Rameshshanker et al. 2016).

Of the four identified studies two were RCTs. These RCTs differed substantially in their generalisability to real world practice. The clinical outcomes reported in the standard colonoscopy arm of the E-CAP study were substantially higher than would be expected in routine clinical practice, whilst the ADENOMA study was more closely aligned with outcomes observed in the real world. This difference in baseline ADR limited the potential benefit of ENDOCUFF VISION® in the E-CAP study and suppressed the true value of ENDOCUFF VISION®. Due to this key difference it was not felt appropriate to synthesise these results and to instead focus on data from the ADENOMA study.

7.9 Interpretation of Clinical Evidence

7.9.1 Provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and any risks relating to adverse events from the technology.

As reported in Section 7.8.2, we note that the E-Cap study reports an unusually high baseline detection rate amongst the endoscopists. In particular, the rates reported are considerably higher than the national average ADR (Logan et al. 2012) and the aspirational target set out by the BSG. Due to this, the results of E-Cap are considered not representative of or generalisable to UK clinical practice. Therefore, the E-Cap study has not been considered any further in this document.

Evidence from one large RCT and two observational studies suggest that the use of ENDOCUFF VISION® is associated with significantly higher ADR, PDR, MAP and CDR compared with standard colonoscopy in patients undergoing screening and surveillance colonoscopies. Although there is

evidence to suggest ENDOCUFF VISION® is also associated with higher detection in diagnostic procedures than standard colonoscopy, the findings are not statistically significant.

Further, evidence across the trials indicate that the use of ENDOCUFF VISION® is associated with faster caecal intubation and withdrawal times.

There were minimal reports of device-related adverse events concerning patient pain or discomfort with the use of ENDOCUFF VISION®.

7.9.2 Provide a summary of the strengths and limitations of the clinical-evidence base of the technology.

All three of the studies considered were conducted in a UK hospital setting. Two studies included patients who had been referred for bowel cancer screening, and the ADENOMA study also included patients referred due to clinical symptoms.

Only the ADENOMA trial had a low risk of bias. This was a large study of 1,772 patients referred for screening, surveillance and diagnostic colonoscopies in a UK hospital setting. Patients were adequately randomised to receive ENDOCUFF VISION® or standard colonoscopy. Patients, colonoscopists and research nurses were not blinded to allocation in this trial. However, the authors reported that all study analyses were conducted in a blinded fashion. Given the nature of the device it was not possible to blind the endoscopist carrying out the procedure and assessing the outcomes, which may introduce some bias. There was no evidence of selective reporting and all patients were included in the analyses.

The two observational studies were deemed to have an unclear risk of bias due to limited reporting of key assessment criteria and the outcome assessors were not blinded. However, due to the nature of these studies, they may be more reflective of routine clinical practice

We note that there is a lack of evidence for the following outcome measures requested in the final scope: miss rate, referral rates and other long-term outcomes (see Section 7.9.3). This is a limitation of the clinical evidence.

7.9.3 Provide a brief statement on the relevance of the evidence base to the scope. This should focus on the claimed patient- and system-benefits described in the scope.

Overall, the population, intervention, comparator and majority of outcomes defined by the scope are captured within the evidence base.

The benefits to patients claimed by the company through the use of ENDOCUFF VISION® colonoscopy are:

- Significantly increased diagnostic yield: more cancerous and pre-cancerous polyps can be identified, potentially enabling earlier detection of cancer:
    - Fully supported by the evidence: the evidence from the three studies considered suggest that the use of ENDOCUFF VISION® is associated with significantly higher ADR, PDR, MAP and cancer detection compared with standard colonoscopy in patients undergoing screening and surveillance colonoscopies. Whilst there is evidence to suggest ENDOCUFF VISION® is also associated with higher detection in diagnostic procedures than standard colonoscopy, the findings are not statistically significant.
- More polyps are fully excised, which may reduce the need to refer patients to more specialist services for expert clinical care or open surgery, which may entail more travelling for the patient:
    - There is no evidence to support this claim. The current evidence base is for detection of growths rather than removal
- Better evaluation of post-excision scars, which may reduce unnecessary repeat procedures and avoid tumour recurrence:

- There is no evidence to support this claim. The current evidence base is for detection of growths rather than removal.

- Greater operator confidence in the colonoscopic procedure: patients may be given more accurate post-procedural information based on higher procedure sensitivity, allowing the correct post-procedural surveillance protocol to be followed and potentially reducing the risk of subsequent cancers or unnecessary procedures.

- Easier access to electrocoagulation for angiodysplasia, potentially reducing the number of repeat colonoscopies:

    - There is no evidence to support this claim

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

- Fewer missed cancers, which may be associated with the treatment of earlier cancers rather than advanced ones, resulting in fewer appointments, less chemotherapy, less radiotherapy, fewer additional tests, reduced inpatient time, less palliative treatment and less litigation:

    - Partially supported: higher detection rate in patients which may lead to more appropriate surveillance intervals.

- Through the better removal of pre-malignant lesions, fewer cancers in the future with substantial savings in staff, consumables, surgery, and other treatments that would have been needed:

    - There is no evidence to support this claim. The current evidence base is for detection of growths rather than removal

- More effective adenoma removals, polyp excisions and electrocoagulation, potentially leading to fewer recurrences or less need for open surgery, follow-ups, tests and treatment as listed above.

There is no evidence to support this claim. The current evidence base is for detection of growths rather than removal.

7.9.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice.

All of the studies evaluated the use of ENDOCUFF VISION® in UK hospital settings and findings were consistent across the studies. Two of the studies (ADENOMA and Tsiamoulos 2018) reported that patients were enrolled from the national BCSP following positive faecal occult blood test. This largely reflects the type of patients who would receive the procedure in clinical practice, meaning the results are generalisable.

The level of endoscopists' experience with ENDOCUFF VISION® varied across the studies. In the ADENOMA trial, 17 of the 48 endoscopists carrying out the procedure were BCSP accredited, however, they were all required to have performed at least 20 colonoscopies with ENDOCUFF VISION® prior to the study. In contrast, in Tsiamoulos 2018, of the four endoscopists carrying out the procedures, only one had experience with ENDOCUFF VISION®.

In Rameshshanker 2016, the authors reported that the endoscopist was experienced, but they do not state whether the endoscopist had prior experience with the device.

7.9.5 Based on external validity factors identified in 7.9.4 describe any criteria that would be used in clinical practice to select patients for whom the technology would be suitable.

The technology can be used in any patient who requires a colonoscopy and who does not have any conditions where the use of ENDOCUFF VISION is contraindicated. The ADENOMA study indicated that the bowel cancer screening population had most benefit in terms of increase in ADR.

Section C – Economic Evidence

Section C requires sponsors to present economic evidence for their technology.

All statements should be evidence-based and directly relevant to the decision problem.

The approach to the de novo cost analysis expected to be appropriate for most technologies is cost-consequence analysis. Sponsors should read Section 7 of the Medical Technologies Evaluation Programme Methods guide on cost-consequences analysis, available from www.nice.org.uk/mt

Sponsors are requested to submit Section C with the full submission. For details on timelines, see the NICE document 'Guide to the Medical Technologies Evaluation Programme process', available from www.nice.org.uk/mt

8 Existing economic evaluations

8.1 Identification of studies

8.1.1 Describe the strategies used to retrieve relevant health economics studies from the published literature and to identify all unpublished data. The search strategy used should be provided as in section 10, appendix 3.

One search was conducted to identify both the clinical and economic evidence relating to the eligible interventions: as this search strategy was not limited by study design it was able to retrieve studies reporting any outcome. See section 7.1 for a full description of the search strategy.

8.1.2 Describe the inclusion and exclusion criteria used to select studies from the published and unpublished literature. Suggested headings are listed in the table below. Other headings should be used if necessary.

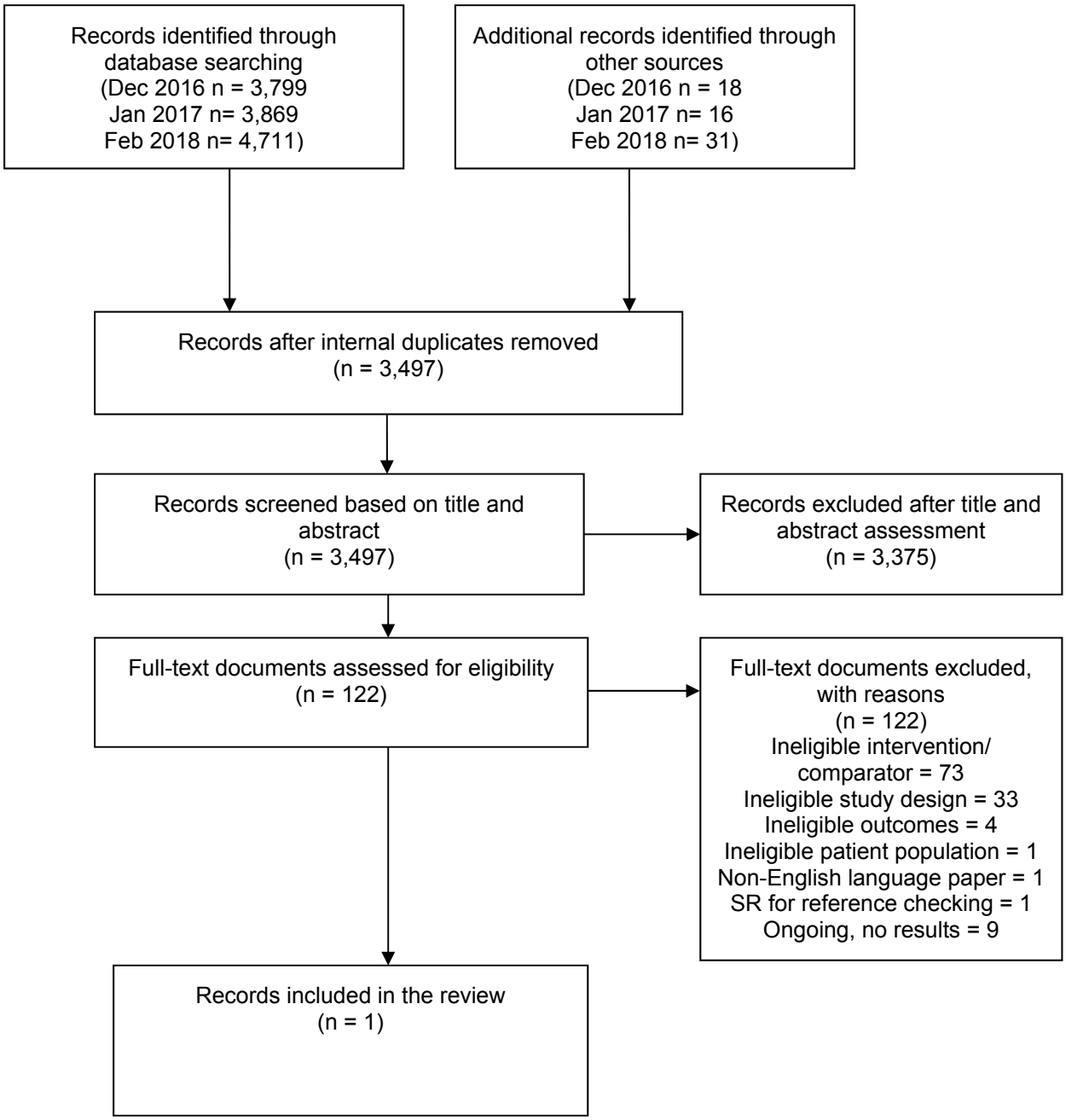
Table C1 Selection criteria used for health economic studies

Inclusion criteria	
Population	Studies of adult (over 18 years of age) patients scheduled for colon screening, colonic surveillance or diagnostic colonoscopy, due to any cause.
Interventions	Studies that evaluate ENDOCUFF VISION® –assisted colonoscopies.
Outcomes	Not specified to maximise sensitivity
Study design	Heath economic studies (ENDOCUFF VISION® v. standard colonoscopy): • Cost-effectiveness; • Cost-utility; • Cost-benefit; • Cost-minimisation; • Cost-consequence.
Language restrictions	• No language limits (although studies reported in languages other than English would not be extracted, but would be listed for information only).
Search dates	• A date limit of 2010 to the current period.
Exclusion criteria	
Population	Studies of patients under the age of 18 or of adult patients that are not scheduled for colon screening, colon surveillance or diagnostic colonoscopy due to any cause.
Interventions	Studies that do not evaluate ENDOCUFF VISION® –assisted colonoscopies
Outcomes	N/A
Study design	Any study design that is not listed in the inclusion criteria including non-comparative cost analyses including cost of illness studies
Language restrictions	N/A
Search dates	Studies published before 2010.

8.1.3 Report the numbers of published studies included and excluded at each stage in an appropriate format.

Study selection was conducted alongside that for the clinical review as reported in Section 7.2.3. The full record selection process for this review is presented as a PRISMA flow diagram in Figure C.1.

Figure C.1: Record selection process for economic studies (PRISMA flow diagram)



8.2 Description of identified studies

8.2.1 Provide a brief review of each study, stating the methods, results and relevance to the scope. A suggested format is provided in table C2.

One study was identified and included within the cost study review. This is detailed in Table C2. The study suggested that the addition of ENDOCUFF VISION® to colonoscopy in German screening patients improves ADR by 11.7% and results in cost savings of €2,829,922 per 10,000 patients or €283 per person. However, as the study was conducted from a German perspective it is of limited relevance to the NHS. Furthermore, this model is not based on ENDOCUFF VISION® clinical data but is based upon an older version of the device (ENDOCUFF).

Table C2 Summary list of all evaluations involving costs

Study name (year)	Location of study	Summary of model and comparators	Patient population	Costs	Patient outcomes	Results
Conway *et al*. (2015) (Conway et al. 2015)	Germany	Treatment = polyethylene glycol + ascorbate (bowel cleansing agent) plus ENDOCUFF VISION®. Comparator = polyethylene glycol + ascorbate Model = decision tree followed by Markov model over a 10 year time horizon.	Cohort of German screening population aged 55 years or above.	Cost of ENDOCUFF VISION® = €30.	Improvement in ADR with ENDOCUFF VISION® = 11.7% (based on ENDOCUFF™ data).	Results were presented incrementally only and based on 10,000 patients. Additional CRC cases prevented = 183 Reduction in CRC cases missed = 12 Cost saving per 10,000 people over 10 years = €2,829,922.

8.2.2 Provide a complete quality assessment for each health economic study identified. A suggested format is shown in table C3.

As the study was published as an abstract and poster only, no formal quality assessment was conducted.

9 De novo cost analysis

Section 9 requires the sponsor to provide information on the de novo cost analysis.

The de novo cost analysis developed should be relevant to the scope.

All costs resulting from or associated with the use of the technology should be estimated using processes relevant to the NHS and personal social services.

Note that NICE cites the price of the product used in the model in the Medical Technology guidance.

9.1 Description of the de novo cost analysis

9.1.1 Provide the rationale for undertaking further cost analysis in relation to the scope.

The only economic analysis of ENDOCUFF VISION® identified in Section 8 was undertaken from a German healthcare perspective and therefore no economic analysis considering the costs of ENDOCUFF VISION® compared with standard colonoscopy from the perspective of the NHS in England and Wales were identified. As a result, it was judged appropriate to undertake a *de novo* cost analysis.

Patients

9.1.2 What patient group(s) is (are) included in the cost analysis?

As described in Section 7.9.1, ENDOCUFF VISION® is associated with significantly higher ADR, PDR, MAP and cancer detection compared with standard colonoscopy in patients undergoing screening and surveillance colonoscopies. Evidence around the use of ENDOCUFF VISION® in diagnostic procedures is not statistically significant. Therefore, the cost analysis is focused on those patients in whom ENDOCUFF VISION® has been demonstrated to be clinically effective: those patients in the ADENOMA

screening and surveillance BCSP population. This is a subgroup specified in the scope.

Technology and comparator

9.1.3 Provide a justification if the comparator used in the cost analysis is different from the scope.

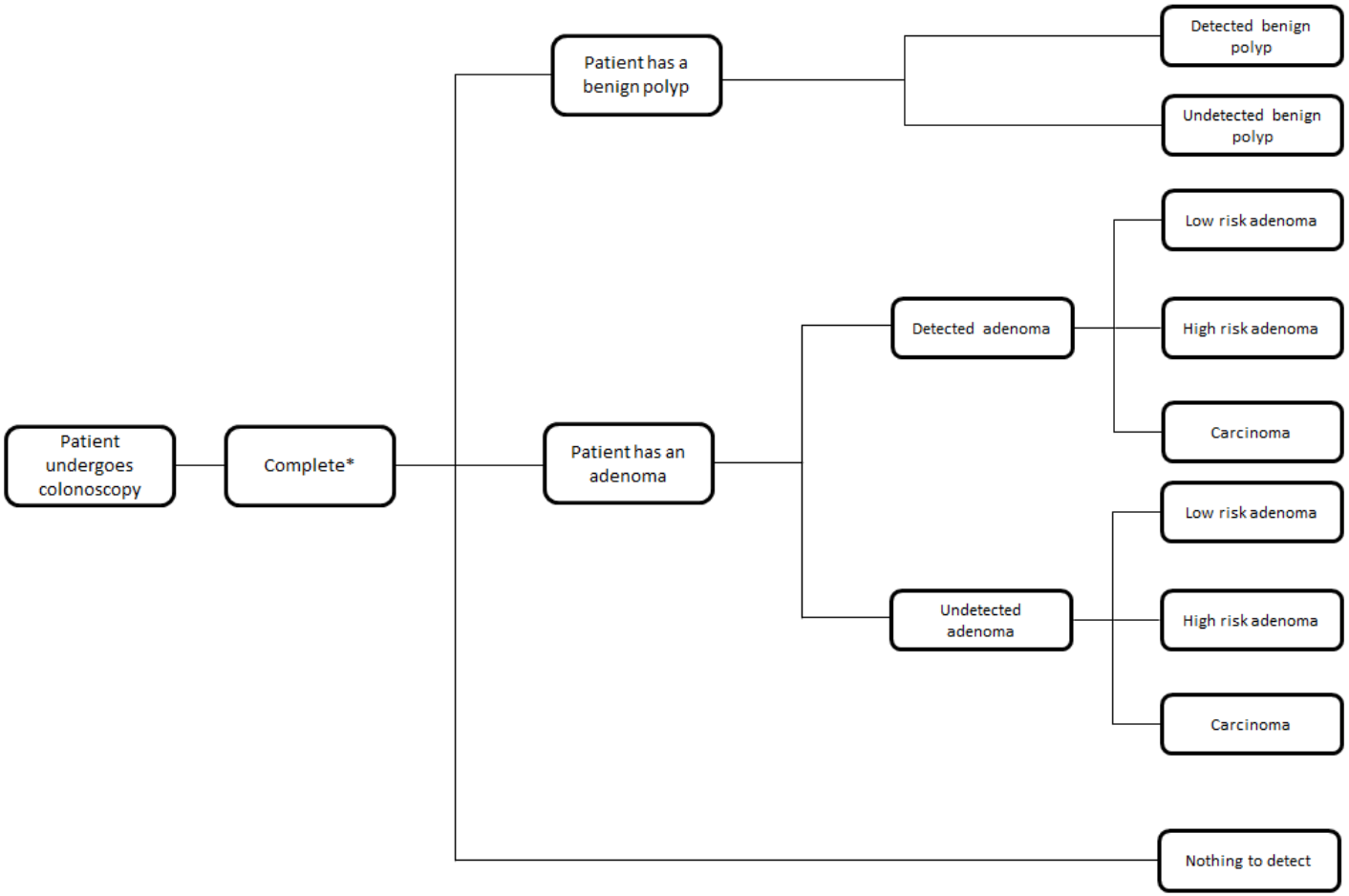
The comparator, standard colonoscopy, used within the cost analysis is aligned with the scope.

Model structure

9.1.4 Provide a diagram of the model structure you have chosen.

The model structure is presented in Figure C.2 (decision tree) and Figure C.3 (Markov model).

Figure C.2: Decision tree element of model



* A small proportion of people have an incomplete colonoscopy. These people are assumed to undergo a second colonoscopy within the same cycle (year). The additional cost of the failed colonoscopy is captured within the model.

Figure C.3: Markov model element of model

The model structure was developed based upon previous published models used to assess the cost-effectiveness of the National Bowel Cancer Screening Programme (Tappenden et al. 2007, Whyte et al. 2012a). The most recent application of this model was published in 2017 (Murphy et al. 2017) and was based upon the previously validated model published by Whyte et al (Whyte et al. 2012a).

A decision analytic model with a 1 year cycle length was developed to compare the cost consequences of colonoscopy with ENDOCUFF VISION® to standard colonoscopy. The model consisted of two elements. First, a decision tree mapping out potential patient pathways following colonoscopy and, second, a Markov element which follows the natural disease progression of all people that underwent an index colonoscopy. Patients in the natural history trace were scheduled for a follow-up colonoscopy according to their risk at index colonoscopy. A cohort of 1,000 hypothetical people enter the model.

All people entering the model undergo a colonoscopy (either standard or with ENDOCUFF VISION®). The majority of colonoscopies are complete. A colonoscopy is defined as being incomplete where the cecum is not reached (Ngu et al. 2018b). Those people with an incomplete index colonoscopy are assumed to undergo a second colonoscopy with the same intervention within the same cycle (year) which is assumed to be complete. The additional cost of the failed colonoscopy is captured within the model. A patient who has a colonoscopy may have a benign polyp, an adenoma or nothing to detect. In the model, benign polyps and adenoma are discrete, such that, if a patient has both a benign polyp and an adenoma they would be classified as having an adenoma only. Adenomas are further categorised as being high risk (incorporating both intermediate and high risk), low risk or cancerous (carcinoma). People with either benign polyps or adenoma may have these detected during the colonoscopy or they may go undetected. The specificity of colonoscopies either with or without ENDOCUFF VISION® was set at 100% in line with previous economic evaluations of colonoscopy (Tappenden et al. 2007, Whyte et al. 2012a). Therefore, the model structure did not incorporate situations in which people had lesions identified, but did not actually have any lesions.

People requiring (and compliant with) surveillance colonoscopies re-enter the model decision tree each year during which their polyps and adenoma (known according to their Markov model health state) may be detected or remain undetected. These are:

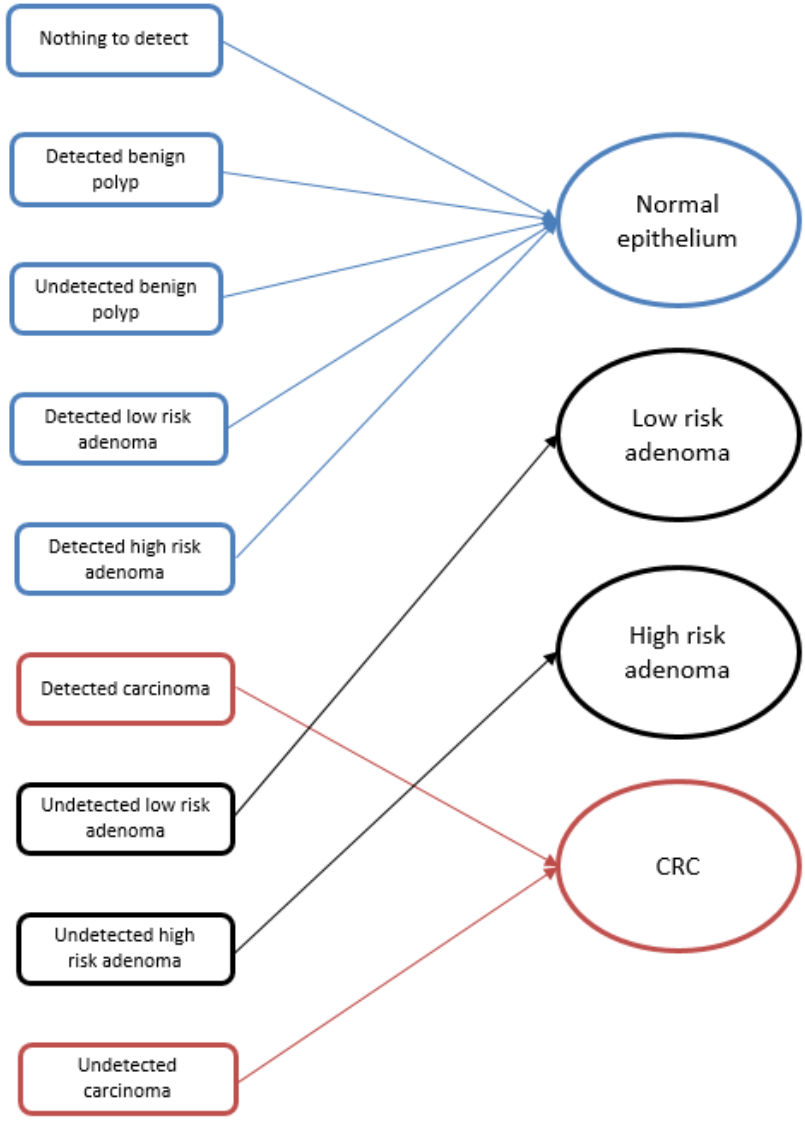
- People with detected intermediate or high risk adenoma – re-enter the decision tree in the following year. This is a simplification of current NICE guidelines on colonoscopic surveillance which includes three categories: low risk, intermediate risk and high risk. In the absence of data for the progression of intermediate risk adenomas previous modelling exercises have grouped intermediate/high risk adenomas into a single state (National Institute for Health and Care Excellence 2011a);
- People with detected low risk adenoma – re-enter the model in 5 years. This is a simplification of current NICE guidelines on colonoscopic surveillance (National Institute for Health and Care Excellence 2011a).

Patients who re-enter the decision tree element of the model do so in the same arm as their first colonoscopy, i.e. those people who have an index colonoscopy with ENDOCUFF VISION® will have a surveillance colonoscopy with ENDOCUFF VISION®. The colonoscopy occurs at the start of the year. The status (i.e. normal epithelium, low risk adenoma etc.) of people re-entering the model is known from the Markov element of the model and as such the purpose of the decision tree in years following index colonoscopy is to determine whether lesions are detected, or not. People with carcinoma do not re-enter the decision tree given that they will undergo surveillance and treatment already included within the applied cost of colorectal cancer.

The Markov element of the model captures the underlying disease progression for all people within the model (Figure C.3). Patients follow a step-wise progression through the model. Those in the normal epithelium health state are at risk of remaining in their current health state or transitioning to low risk-adenoma. From the low-risk adenoma health state patients transition to high-risk adenoma or remain in their current health state. In the high risk health state patients can develop CRC. When patients develop CRC they are apportioned into either CRC mortality or post-CRC.

The underlying progression pathway and probabilities are the same in both the treatment and comparator arms of the model. However, the number of people moving into each health state within the Markov part of the model will differ by treatment type. This is displayed in Figure C.4 and described below.

Figure C.4: Movement from decision tree to Markov model (at start of cycle 1)



People enter the Markov element of the model in the following health states:

- People with nothing to detect following a complete colonoscopy. These people enter the 'normal epithelium' health state and undergo faecal occult blood test (FOBT) screening every 2 years
- People with benign polyps (undetected or detected) following a complete colonoscopy. These people enter the 'normal epithelium' health state and undergo FOBT screening every 2 years

- People with undetected low risk adenoma following a complete colonoscopy. These people enter the ‘low risk adenoma’ health state
- People with undetected high risk adenoma following a complete colonoscopy. These people enter the ‘high risk adenoma’ health state
- People with undetected carcinoma enter the CRC health state as these people are assumed to have their CRC detected within the same cycle
- People with detected low or high risk adenoma enter the normal epithelium health state, given that the adenomas are removed during the colonoscopy. However, these people are at a higher risk of developing further lesions than the rest of the population. This increased risk is applied until they have a surveillance colonoscopy indicating no adenoma. Tunnel states are used to track which people had high risk or low risk adenoma. The transition probabilities applied within each tunnel state are equal across all risk-categories, however, the use of tunnel states allows patients to be tracked and undergo a repeat (surveillance) colonoscopy at the correct time.
- People with detected carcinoma enter the CRC health state.

Those people moving into the CRC health state in year 2 onwards are assumed to have their CRC detected as a result of symptoms, rather than through the surveillance programme, hence patients transitioning into this health state always have the cost of CRC resulting from missed lesions applied (Section 9.3). This is assumed because these patients do not enter the surveillance programme due to having no adenomas detected. Patients that develop CRC after the first year are apportioned into those that eventually die from CRC and those that survive (but will eventually die from other causes). This simplification removes the need to model long-term cancer outcomes for these patients. Costs are applied as a one-off cost and capture lifetime costs for patients in these states. All-cause mortality is applied on an annual basis and is applied independently to the other transition probabilities within the model.

9.1.5 Justify the chosen structure in line with the clinical pathway of care identified in response to question 3.3.

The model structure captures outcomes for patients undergoing a colonoscopy as shown in Figure A3. There are a number of reasons why patients may undergo a colonoscopy and the model focuses on those patients having a colonoscopy in the BCSP (i.e. screening or surveillance). Colonoscopy is associated with a number of potential outcomes. These have been incorporated into the model structure which has been validated through KOL interviews as detailed in Section 9.2.5. Once a patient undergoes a colonoscopy, they enter one of the following categories (as shown in Figure A3):

- CRC detected. These patients enter the CRC health state and subsequent post-CRC or dead health states.
- Adenomas detected. These patients undergo surveillance and re-enter the model after a specified time.
- Nothing detected. These patients (particularly those with missed adenoma which may transition into CRC) are explicitly captured within the model. Screening patients continue to have a FOBT every 2 years.
- Non-cancer/non-adenoma condition detected. This is not captured within the model as there is no clinical evidence for ENDOCUFF VISION® reporting on this.

The transition of patients over time in the Markov element of the model is aligned with previous economic evaluations in this area conducted for the NHS bowel cancer screening programme (Murphy et al. 2017, Whyte et al. 2012a) and previous NICE guidance (Picot et al. 2017). In the Markov model, the transition probabilities applied are the same across treatment arms (i.e. no treatment effect). However, the number of patients entering each health state within the Markov model is determined by the efficacy of diagnosis. A simplification has been made in this model compared to previous published

models in that patients with CRC of all stages are combined within one health state. However, the cost applied to these patients is weighted according to stage of CRC at diagnosis.

9.1.6 Provide a list of all assumptions in the cost model and a justification for each assumption.

Table C3: Modelling assumptions

Assumption	Justification
A half cycle correction is applied to the Markov trace except in the first cycle.	This is applied to capture that on average patients' transition between health states half way through the year. In the first cycle, the whole cohort of patients undergo a colonoscopy at the start of the model and hence this is not half cycle corrected. Doing so would underestimate the number of patients with cancer in the first cycle.
People with multiple types of lesions are classified by their 'worst' detected lesion, i.e. a person with 5 or more small adenomas or 3 or more large adenomas and benign polyps would be classed as having high risk adenoma. This also defines their follow up interval.	This is aligned with the patient risk group reported in the ADENOMA study (Ngu et al. 2018b).
Patients with intermediate risk are classified with the high risk group	This assumption is in line with previous models from which transition probabilities are taken (Whyte et al. 2012a).
People with incomplete colonoscopies are assumed to undergo another colonoscopy within the same cycle. The cost of a colonoscopy has been scaled up accordingly to account for patients requiring multiple colonoscopies; hence, the cost of incomplete colonoscopies is an average of the cost of a colonoscopy with and without detection weighted by the proportion of patients with detected lesions.	Clinical experts advised that where a colonoscopy is incomplete, a further colonoscopy or other alternative test will be offered. The assumption that all follow-up tests are colonoscopies has a limited impact on the model given the negligible difference in incomplete colonoscopies between arms. Alternative tests include a CT scan which is more expensive than a colonoscopy.
People with undetected colorectal cancer are assumed to have this detected outside of the colonoscopy and incur all cancer costs within the same cycle (i.e. within a year).	Laudicella et al. report that around 50% of health care costs (over a 9 year period) are incurred in the year of CRC diagnosis. However, this paper refers to all healthcare costs (not those specific to CRC) (Laudicella et al. 2016). The costs incurred in the year following diagnosis (according to Laudicella et al.), i.e. first year only fall within the range of the CRC costs used in the model. This assumption is explored during sensitivity analyses.
People with detected carcinoma have lower costs of cancer treatment than those with undetected carcinoma in line with the published literature.	This assumption is based upon published literature from Germany (Wiegering et al. 2016). CRC costs were previously presented to KOLs and no objections were raised as to weighting of these costs. See Section 9.2.5.

Assumption	Justification
People with colorectal cancer can only die from colorectal cancer in the year that they enter the colorectal cancer health state.	This simplifying assumption has a very limited impact on the results of the model as a lifetime risk is applied. Thus we are not underestimating the total number of deaths, just varying when they occur.
People with CRC in years 2 onwards are assumed to be symptomatic and diagnosed outside of the surveillance scheme.	These people transition from undetected high risk adenoma and hence would not be undergoing regular colonoscopy surveillance. A small proportion of patients with undetected cancer could experience a positive FOBT and undergo a colonoscopy. However, this assumption has been made for simplification given that the proportion of patients with CRC after year 1 is already very small.
People who have an adenoma are at higher risk of a second adenoma in subsequent years, until they have a surveillance colonoscopy indicating that they have no adenoma. This recurrence is assumed to be low risk, until it converts to high risk.	This is aligned with previous models developed for the NHS bowel cancer screening programme (Tappenden et al. 2007).
All-cause mortality has not been adjusted for colorectal cancer mortality.	This simplifying assumption has a very limited impact on the results of the model.
A learning curve effect with ENDOCUFF VISION® is applied	There may be reduced efficacy, relative to an experienced ENDOCUFF VISION® user, for less experienced clinicians. This has been explored in the model via the learning curve effect whereby it has been conservatively assumed there is no improvement in efficacy for the first 20 colonoscopies completed by each colonoscopist with ENDOCUFF VISION® compared to standard colonoscopy (Ngu et al. 2018b).(Shenbagaraj et al. 2018, Marsano et al.)

9.1.7 Define what the model's health states are intended to capture.

The model's health states and what they are intended to capture is described below:

Decision tree

- Detected polyp captures those patients who have had a polyp identified and removed.
- Undetected polyp captures those patients who have a polyp which was not identified during their colonoscopy.

- Low risk detected adenoma captures those patients with a low risk adenoma which was identified and removed during their colonoscopy.
- High risk detected adenoma captures those patients with a high risk adenoma which was identified and removed during their colonoscopy.
- Detected carcinoma captures those patients with colorectal cancer who have had this identified during their colonoscopy.
- Undetected low risk adenoma captures those patients who have a low risk adenoma but have not had it identified during their colonoscopy.
- Undetected high risk adenoma captures those patients who have a high risk adenoma but have not had it identified during their colonoscopy.
- Undetected carcinoma captures those patients with colorectal cancer but have not had it identified during their colonoscopy.
- Nothing to detect captures those patients who do not have any polyps or adenomas and therefore had nothing detected during their colonoscopy.

Markov model

- Normal epithelium health state captures those patients with no adenoma or carcinoma, or patients who have had adenomas identified and removed.
- Undetected low risk adenoma health state captures those patients with low risk adenoma that were either not detected during their colonoscopy or have developed since.
- Undetected high risk adenoma health state captures those patients with high risk adenoma that were either not detected during their colonoscopy or have developed since.
- CRC health state captures those patients with cancer. Patients enter this health state either from a diagnosis following a colonoscopy (lower cost

applied) or via developing cancer as a result of missed adenoma that become cancerous (higher cost applied).

- Post-CRC health state is where patients move in the cycle after being diagnosed with cancer. It is assumed that these patients are followed up outside of the screening programme hence they remain in this health state for the rest of the model timeframe unless they die as a result of all-cause mortality.
- CRC mortality health state captures those who have died from CRC.
- All-cause mortality health state captures those who have died from other causes.

9.1.8 Describe any key features of the cost model not previously reported. A suggested format is presented below.

Table C4 Key features of model not previously reported

Factor	Chosen values	Justification	Reference
Time horizon of model	10 years	This time horizon was selected given that patients would be expected to have a repeat colonoscopy after 10 years. This horizon captures the costs associated with higher detection requiring increased surveillance. Extrapolating beyond 10 years was judged to introduce too much uncertainty.	
Discount of 3.5% for costs	3.5% per year	In line with MTEP methods guide	NICE 2017 (National Institute for Health and Care Excellence (NICE) 2017)
Perspective (NHS/PSS)	NHS/PSS perspective	In line with MTEP methods guide	NICE 2017 (National Institute for Health and Care Excellence (NICE) 2017)
Cycle length	Annual	This allows patients to re-enter the diagnostic element of the model each cycle (annually) aligned with clinical practice.	
NHS, National Health Service; PSS, Personal Social Services			

9.2 Clinical parameters and variables

9.2.1 Describe how the data from the clinical evidence were used in the cost analysis.

Adenoma detection rate and benign polyp detection rate were used from the ADENOMA trial (Ngu et al. 2018b) for both ENDOCUFF VISION® and standard colonoscopy. The rates for the screening (BCSP) population were used in the base case. The proportion of patients having a successful colonoscopy and the breakdown of detected adenoma into risk categories was also taken from the ADENOMA trial. To split detected adenoma into the risk groups in the model reported intermediate risk was combined with reported high risk, and then reported carcinoma subtracted from this figure to calculate the proportion of high risk adenoma. Carcinomas are not reported cumulatively alongside adenomas.

The non-randomised data identified in Section 7 are not used within the model.

9.2.2 Are costs and clinical outcomes extrapolated beyond the study follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified?

The clinical studies are used for the decision tree element of the model in order to split the population. Due to differences in the detection rates for colonoscopy with ENDOCUFF VISION® and standard colonoscopy the split of the patient group differs between arms (as aligned with the ADENOMA study (Ngu et al. 2018b)). This split is used to inform the health state to which patients enter the Markov model and therefore the long-term benefits demonstrated in the ADENOMA study are captured in the Markov model. The extrapolation of the natural history of the disease over time is independent of the device used for colonoscopy and is based on the patient progression model that has been applied in previous economic evaluations of the National Bowel Cancer Screening Programme (Murphy et al. 2017, Whyte et al. 2012a).

9.2.3 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used and what other evidence is there to support it?

Intermediate outcomes from colonoscopy were linked to long-term outcomes. The relationship between detection and downstream consequences were modelled according to published estimates of disease progression that have been applied in previous modelling evaluations of the BCSP. The relationship between detection during colonoscopy and improved outcomes for patients has been published by Corley et al who demonstrated a 1% increase in ADR resulted in a 3% decrease in the risk of cancer (Corley et al. 2014b).

Undetected low risk and high risk adenoma were subject to an annual transition probability to determine the likelihood of becoming cancerous. These data were derived from the published literature.

The true adenoma and benign polyp rates were estimated using the sensitivity of a colonoscopy in detecting these lesions. As a result of the lack of a gold standard test reporting on the true adenoma and benign polyp rates, the sensitivity of colonoscopy (with or without ENDOCUFF VISION®) was assumed to be 100% for the test which performed best. Whilst this will impact on the total costs in each arm, there will be no impact on the incremental costs and cost savings.

9.2.4 Were adverse events such as those described in section 7.7 included in the cost analysis? If appropriate, provide a rationale for the calculation of the risk of each adverse event.

No device-specific adverse events were reported and no difference in adverse events were reported between the two treatment arms in the primary clinical

study, the ADENOMA study (Ngu et al. 2018b), consequently adverse events were not explicitly modelled, however, the proportion of unsuccessful colonoscopies was incorporated into the model. An additional cost was applied to patients having an unsuccessful colonoscopy to account for a repeat colonoscopy, but no further costs were incurred, so any costs additional to the cost of a colonoscopy would not be captured. The probability of successful colonoscopy was taken from Ngu et al 2018 (Ngu et al. 2018b).

9.2.5 Provide details of the process used when the sponsor's clinical advisers assessed the applicability of available or estimated clinical model parameter and inputs used in the analysis.

[redacted]

[redacted]

[redacted]

9.2.6 Summarise all the variables included in the cost analysis. Provide cross-references to other parts of the submission. A suggested format is provided in table C5 below.

Table C5 Summary of variables applied in the cost model

Variable	Value	Range or 95% CI (distribution)	Source
Starting age	62 years	NR	Ngu et al 2018 (Ngu et al. 2018b)
Proportion of men	57.0%	NR	Ngu et al 2018 (Ngu et al. 2018b)
Discount rate (costs)	3.5%	NA	NICE 2017 (National Institute for Health and Care Excellence (NICE) 2017)
High risk – years between colonoscopy	1 year	NA	Simplification of NICE guidelines (National Institute for Health and Care Excellence 2011a)
Low risk – years between colonoscopy	5 years	NA	Simplification of NICE guidelines (National Institute for Health and Care Excellence 2011a)
Compliance with surveillance	83%	NR	Whyte et al 2012 (Whyte et al. 2012a)
Compliance with FOBT screening	85%	NR	Whyte et al 2012 (Whyte et al. 2012a)
Compliance with colonoscopy after FOBT screening	79%	0.79 to 0.79 (CI)	Whyte et al 2012 (Whyte et al. 2012a)
Proportion of successful colonoscopies (ECV)	97.7%	Difference between ECV and SC: -0.1%, 97.5% CI for difference: -2.1% to ∞	Ngu et al 2018 (Ngu et al. 2018b)
Proportion of successful colonoscopies (SC)	97.8%		Ngu et al 2018 (Ngu et al. 2018b)
Adenoma detection rate (ECV)	61.7%	Difference between ECV and SC: 10.8% 97.5% CI for difference: 5.1% to ∞	Ngu et al 2018 (Ngu et al. 2018b)
Adenoma detection rate (SC)	50.9%		Ngu et al 2018 (Ngu et al. 2018b)
Benign polyp detection rate (ECV)	12.2%	Difference between ECV and SC: 0.2% 97.5% CI for difference: 0.1% to ∞	Ngu et al 2018 (Ngu et al. 2018b)
Benign polyp detection rate (SC)	12.4%		Ngu et al 2018 (Ngu et al. 2018b)
True adenoma rate	61.7%	NA	Assumption based upon 100% sensitivity for the better performing option
True benign polyp rate	12.4%	NA	Assumption based upon 100% sensitivity for the

Variable	Value	Range or 95% CI (distribution)	Source
			better performing option
FOBT screening - Probability of requiring a colonoscopy: normal	0.5%	NR	Calculation based on specificity in Whyte et al 2012 (Whyte et al. 2012a)
FOBT screening - Probability of requiring a colonoscopy: low risk adenoma	1.0%	NR	Calculation based on sensitivity and specificity in Whyte et al 2012 (Whyte et al. 2012a)
FOBT screening - Probability of requiring a colonoscopy: high risk adenoma	6.5%	NR	Calculation based on sensitivity and specificity in Whyte et al 2012 (Whyte et al. 2012a)
Proportion with no detected adenoma (ECV)	38.3%	p value 0.004	Ngu et al 2018 (Ngu et al. 2018b)
Proportion with no detected adenoma (SC)	49.1%		
Proportion of detected adenoma - low risk (ECV)	34.5%	NR	
Proportion of detected adenoma - low risk (SC)	27.8%	NR	
Proportion of detected adenoma - high risk (ECV)	20.6%	NR	
Proportion of detected adenoma - high risk (SC)	19.4%	NR	
Proportion of detected adenoma - carcinoma (ECV)	6.6%	Difference between ECV and SC: 2.9% 97.5% CI for difference: 0.3% to ∞	
Proportion of detected adenoma - carcinoma (SC)	3.7%		
Proportion of undetected adenoma - low risk (ECV)	56.0%	NA	Assumed to be equal to detected low risk adenoma. This is only applied due to the learning curve effect which reduces the sensitivity of ECV from 100%.
Proportion of undetected adenoma - high risk (ECV)	33.3%	NA	Assumed to be equal to detected high risk adenoma. This is only applied due to the learning curve effect which reduces the sensitivity of ECV from 100%.
Proportion of undetected adenoma - carcinoma (ECV)	10.7%	NA	Assumed to be equal to detected carcinoma. This is only applied due to the learning curve

Variable	Value	Range or 95% CI (distribution)	Source
			effect which reduces the sensitivity of ECV from 100%.
Proportion of undetected adenoma - low risk (SC)	62.2%	NA	Calculation: Total low risk adenoma (detected and undetected in ECV arm – detected low risk adenoma in SC arm) / total undetected adenoma in SC arm
Proportion of undetected adenoma - high risk (SC)	11.1%	NA	Calculation: Total high risk adenoma (detected and undetected in ECV arm – detected high risk adenoma in SC arm) / total undetected adenoma in SC arm
Proportion of undetected adenoma - carcinoma (SC)	26.6%	NA	Calculation: Total carcinoma (detected and undetected in ECV arm – detected carcinoma in SC arm) / total undetected adenoma in SC arm
Normal epithelium to low risk adenoma (annual transition)	2.0%	0.019 to 0.021 (model calibration CI)	Whyte et al 2012 (Whyte et al. 2012a)
Low risk adenoma to high risk adenoma (annual transition)	0.8%	0.006 to 0.008 (model calibration CI)	Whyte et al 2012 (Whyte et al. 2012a)
High risk adenoma to CRC (annual transition)	Age 55-59: 2.60% Age 60-64: 3.24% Age 65-69: 4.14% Age 70-74: 4.46% Age 75-79: 5.06% Age 80-84: 5.32%	NR	Brenner et al 2007 (Brenner et al. 2007)
Probability of adenoma recurrence given history of low risk adenoma (year 1)	18%	NR	Tappenden et al 2007 (Tappenden et al. 2007)
Probability of adenoma recurrence given history of low risk adenoma (year 2+)	5%	NR	Tappenden et al 2007 (Tappenden et al. 2007)
Probability of adenoma recurrence given history of	25%	NR	Tappenden et al 2007 (Tappenden et al. 2007)

Variable	Value	Range or 95% CI (distribution)	Source
high risk adenoma (year 1)			
Probability of adenoma recurrence given history of high risk adenoma (year 2+)	6%	NR	Tappenden et al 2007 (Tappenden et al. 2007)
CRC mortality (annual transition) (average of male and female)	20.8%	Male: 19.9%, CI 19.3% to 20.6% Female: 22.1% CI 21.4% to 22.8%	McPhail et al 2015 (McPhail et al. 2015)
Cost of ENDOCUFF VISION®	£12.05	Not varied	Norgine
Cost of colonoscopy without identification of polyps	£547.67	Lower quartile cost: £424 Upper quartile cost: £627	NHS reference costs 2016-17 (NHS Improvement 2017)
Cost of colonoscopy with identification of polyps	£650.92	Lower quartile cost: £523 Upper quartile cost: £759	NHS reference costs 2016-17 (NHS Improvement 2017)
FOBT cost of test: non-compliers	£2.19	Range: £1.96 to £2.39	Whyte et al 2012 (Whyte et al. 2012a). Inflated to 2016/17 prices.
FOBT cost of test: normal result	£3.59	Range: £3.24 to £3.96	Whyte et al 2012 (Whyte et al. 2012a) Inflated to 2016/17 prices.
FOBT cost of test: positive result	£12.77	Range: £11.49 to £14.05	Whyte et al 2012 (Whyte et al. 2012a) Inflated to 2016/17 prices.
Multiplier to account for people having more than 1 FOBT each	1.08	Not varied	Whyte et al 2012 (Whyte et al. 2012a)
Cost of CRC treatment - patients identified through colonoscopy	£9,073	NR	Incisive health 2014 (Incisive Health 2014) weighted by proportion of patients in each stage from Wiegering et al 2016 (Wiegering et al. 2016)
Cost of CRC treatment - patients developing CRC from missed detection	£10,706	NR	Incisive health 2014 (Incisive Health 2014) weighted by proportion of patients in each stage from Wiegering et al 2016 (Wiegering et al. 2016)
Number of training colonoscopies (with ECV)	126	NR	Calculated from number of colonoscopies required for training from (Marsano et

Variable	Value	Range or 95% CI (distribution)	Source
			al.)Ngu et al (Ngu et al. 2018b), and number of operators from Shenbagaraj et al. 2018(Vijan et al. 2004) (Shenbagaraj et al. 2018)
Age related mortality (England and Wales)	Varies by age	Not varied	Office for National Statistics, English life tables 2010-2012 (Office for National Statistics 2016)
CI, confidence interval; ECV, ENDOCUFF VISION®; SC, standard colonoscopy			

9.3 Resource identification, measurement and valuation

NHS costs

9.3.1 Describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff.

Colonoscopies are conducted under the codes reported below.

National Schedule of Reference Costs 2016-17:

- FE30Z - Therapeutic Colonoscopy, 19 years and over
- FE31Z - Diagnostic Colonoscopy with Biopsy, 19 years and over
- FE32Z - Diagnostic Colonoscopy, 19 years and over

Payment by Results Tariff: Annex A 2017/18 National Prices and National Tariff Workbook:

- FZ51Z - Diagnostic Colonoscopy, 19 years and over
- FZ52Z - Diagnostic Colonoscopy with Biopsy, 19 years and over
- FZ53Z - Therapeutic Colonoscopy, 19 years and over

The cost of ENDOCUFF VISION® is currently funded by NHS England under the innovation and technology payment.

9.3.2 State the Office of Population, Censuses and Surveys Classification of Surgical Operations and Procedures (OPCS) codes for the operations, procedures and interventions relevant to the use of the technology for the clinical management of the condition.

OPCS codes:

- H18.1 – Open colonoscopy

Resource identification, measurement and valuation studies

9.3.3 Provide a systematic search of relevant resource data for the NHS in England. Include a search strategy and inclusion criteria, and consider published and unpublished studies.

A pragmatic literature search was designed in Ovid MEDLINE to identify lifetime CRC costs from an NHS perspective. The search was originally carried out in January 2017 and updated in February 2018.

The MEDLINE strategy comprised the following concepts:

- Colorectal cancer

  AND

- Economic evaluations or cost studies. This concept is largely formed by the Canadian Agency for Drugs and Technologies in Health (CADTH) search filter designed to identify economic evaluations and cost data in Ovid MEDLINE (CADTH 2016). The filter is supplemented by some focused terms to identify resource use studies.

  AND

- The National Institute for Health and Care Excellence (NICE) 2016 MEDLINE UK geographic search filter (National Institute for Health and Care Excellence (NICE) 2016).

The search strategy removed animal studies from MEDLINE using a standard algorithm and also excluded publication types which were unlikely to yield relevant information; comments, editorial, news, case reports and letters. The results are limited to English language studies published since 2007.

The MEDLINE strategy was appropriately translated to run in the additional resources searched: Embase (Ovid), and EconLit (Ovid).

Additional searches of relevant organisational webpages and an internet search engine (Google) were also undertaken to identify unpublished or grey literature.

Full, reproducible search strategies and result numbers are reported in Section 10.4, Appendix 4.

The search results were assessed and those studies meeting the following criteria were included:

- Reporting overall CRC (i.e. those studies reporting annual CRC were excluded);
- Costs broken down by stage of cancer and costs on all four stages to be provided;
- Overall NHS/NHS and PSS perspective (i.e. those studies reporting hospital costs or primary care costs only were excluded).

The original search (2017) returned 1169 records, 863 of which represented unique records and remained after duplicates were removed.
An additional 163 unique records (from a total of 1361 records) were identified when the database searches were updated in February 2018
A further 34 records were retrieved by searching relevant webpages and Google for "grey" or unpublished literature.

863 unique records were identified through database searching (1169 before deduplication) and a further 18 via the grey literature giving a total of 881 records. Based on the title and abstract screening 814 records were excluded, meaning 67 full papers were screened. Of these, 12 papers met the inclusion criteria (reporting on 11 studies) and are reported in Table C5b.

Table C5b: CRC costs reported in the literature (all costs inflated to 2016/17 prices)

Author	Year	Description of paper	Price year	Original source for costs	Stage 1	Stage 2	Stage 3	Stage 4	Notes
Incisive health (Incisive Health 2014)	2014	Cancer research UK cost study	NR, appears to be 2013/14	Original costing	£4,451	£9,954	£14,169	£12,797	
EEPRU (Whyte et al. 2012b)	2012	EEPRU costs are original costs.	2012/13	Unclear	£4,829	£5,589	£7,582	£6,798	Costs reported for age 60 to 69
Lee (Lee 2010)	2010	CE analysis of CT colonography for NHS screening patients	2007	Tappenden (Tappenden et al. 2007)	Symptomatic = £9,929 Screening = £8,462	£15,643	£24,474	£16,729	
NICE - NG12 (National Institute for Health and Care	2015	NICE guideline	2012/13	Tappenden (Tappenden et al. 2007)	£8,650	£14,587	£23,599	£15,704	Costing statement reports costs from Incisive Health (2014)

Author	Year	Description of paper	Price year	Original source for costs	Stage 1	Stage 2	Stage 3	Stage 4	Notes
Excellence 2015)									
Public Health England (Public Health England 2016)	2016	Return on investment calculator	2015	Tappenden (Tappenden et al. 2004)	£4,211	£8,240	£10,689	£13,429	Note these are screening costs; emergency and elective costs also reported
NICE - CG118 (National Institute for Health and Care Excellence 2011a)	2011	NICE clinical guideline	NR, appears to be 2010	Tappenden (Tappenden et al. 2007) and updated using personal correspondence with Tappenden and Pilgrim in 2010	£13,073	£17,726	£22,980	£26,326	
Dept. of Health (Department of Health 2011)	2011	Analysis of earlier diagnosis of CRC	2009	Cost reported to be based on ScHARR (so likely either Tappenden/Whyte)	£10,327	£15,758	£24,460	£15,108	
Westwood (Westwood et al. 2017)	2017	Health Technology Assessment report: Faecal immunochemical tests based on NICE diagnostic appraisal	2014/15	Tappenden (Tappenden et al. 2007)	£11,016	£18,576	£30,054	£20,000	

Author	Year	Description of paper	Price year	Original source for costs	Stage 1	Stage 2	Stage 3	Stage 4	Notes
Whyte (Whyte et al. 2012a)	2012	Updated appraisal of screening programmes in England	Used PSSRU 2009 to inflate costs	Unclear (potentially Pilgrim (Pilgrim et al. 2009))	£14,102	£19,403	£26,609	£29,101	These are reported as screen detected costs
Picot (Picot et al. 2017) (NICE report for virtual chromoendoscopy)	2016 /17	NICE diagnostic appraisal	2014/15	Pilgrim (Pilgrim et al. 2009)[2]	£4,833	£5,593	£7,588	£6,803	Costs for 60-69 years

[2] Although both sources indicate that the costs were taken from Pilgrim et al. the costs reported vary widely and these could not be verified Pilgrim H, Tappenden P, Chilcott J, et al. (2009) The costs and benefits of bowel cancer service developments using discrete event simulation. *Journal of the Operational Research Society* 60(10)**,**pp. 1305-1314.. There does not appear to be any discussion around the CRC costs used in DG28: virtual chromoendoscopy to assess colorectal polyps during colonoscopy. Likewise, Murphy et al. did not discuss why the Pilgrim costs were used Murphy J, Halloran S and Gray A (2017) Cost-effectiveness of the faecal immunochemical test at a range of positivity thresholds compared with the guaiac faecal occult blood test in the NHS Bowel Cancer Screening Programme in England. *BMJ Open* 7(10), Pilgrim H, Tappenden P, Chilcott J, et al. (2009) The costs and benefits of bowel cancer service developments using discrete event simulation. *Journal of the Operational Research Society* 60(10)**,**pp. 1305-1314..

Author	Year	Description of paper	Price year	Original source for costs	Stage 1	Stage 2	Stage 3	Stage 4	Notes
Murphy (Murphy et al. 2017)	2017	Cost-effectiveness of two faecal tests in the NHS Bowel Cancer Screening Programme in England	2015/16	Pilgrim (Pilgrim et al. 2009)[2] Whyte (Whyte et al. 2012b)	£14,014	£19,281	£26,443	£28,919	

Table C5b reports CRC costs by stage from 11 sources. These costs represent the total cost of CRC by stage (i.e. lifetime rather than annual costs). It is evident from this table that there is large variation in the estimation of CRC costs by stage. It was judged that the two more recent original costing reported by Incisive Health and EEPRU are most likely to be representative of the cost of CRC to the NHS today. However, the EEPRU (Whyte et al. 2012b) costs do not include recurrence costs and are therefore likely to be an underestimate of overall costs and as a result, the Incisive Health cost was used in the base case. This source represents the most recent original costing and includes recurrence costs which are not captured elsewhere in the model. Further, the Incisive Health costs were used by NICE in its costing statement for a recent clinical guideline and thus were deemed appropriate by the NICE costing team (National Institute for Health and Care Excellence 2015). Alternative costs are considered in scenario analyses.

The costs of CRC were weighted according to stage at diagnosis. Patients with detected CRC were distributed across stage at diagnosis observed in the screening population, with patients with undetected cancers distributed across cancer stages observed in symptomatic detection. Three sources were identified that reported the distribution across cancer stage at diagnosis in the screening and symptomatic population. All three sources reported a trend to an earlier stage of diagnosis of CRC in the screening programme compared to CRC that is detected in the symptomatic population. Wiegering et al. reported the stage at diagnosis for n=1,016 for screen detected and symptomatic detected CRC patients from a single centre in Germany (Wiegering et al. 2016). These patients evaluated in the analysis were the most closely matched to those in the ADENOMA study based upon their age at diagnosis and therefore this study was used in the base case. Whilst Sagar et al. reported data from England, the patients included for symptom detected CRC were older than those in the ADENOMA study (72 years) and the paper was published as an abstract only (Sagar et al. 2015). A scenario analysis was conducted using this data (Section 9.5.7). Finally, an alternative source from the Netherlands was considered in sensitivity analysis only (Toes-Zoutendijk et al. 2017). All sources are presented in Table C5c.

Table C5c: Cancer stage at diagnosis

	Screen detected	Symptomatic detected
Wiegering et al. (Wiegering et al. 2016)		
Dukes stage A	31.3%	18.0%
Dukes stage B	29.9%	32.0%
Dukes stage C	28.4%	23.4%
Dukes stage D	10.4%	26.6%
Sagar et al. (Sagar et al. 2015)		
Dukes stage A	45%	15%
Dukes stage B	28%	31%
Dukes stage C	25%	35%
Dukes stage D	2%	19%
Toes-Zoutendijk et al. (Toes-Zoutendijk et al. 2017)		
Dukes stage A	48.2%	16.7%
Dukes stage B	18.5%	23.1%
Dukes stage C	27.2%	34.6%

Dukes stage D	6.1%	25.7%

The validation exercise conducted in 2016 discussed the validity of costing based on weighted according to stage at diagnosis reported by Wiegering et al. The costs presented were considered to be reflective of the costs of these patients to the NHS (section 9.2.5).

The cost of colonoscopy was obtained from NHS reference costs (NHS Improvement 2017) and the costs relating to FOBT from a published economic evaluation (Whyte et al. 2012a).

9.3.4 Provide details of the process used when clinical advisers assessed the applicability of the resources used in the model[3].

1. [redacted]

[redacted]

[3] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

Technology and comparators' costs

9.3.5 Provide the list price for the technology.

ENDOCUFF VISION® is sold at a price of £12.05.

9.3.6 If the list price is not used in the de novo cost model, provide the alternative price and a justification.

N/A.

9.3.7 Summarise the annual costs associated with the technology and the comparator technology (if applicable) applied in the cost model. A suggested format is provided in tables C6 and C7. Table C7 should only be completed when the most relevant UK comparator for the cost analysis refers to another technology.

Table C6 Costs per treatment/patient associated with the technology in the cost model

Items	Value	Source
Price of the technology per treatment/patient	£12.05	Norgine
Consumables (if applicable)	N/A	N/A
Maintenance cost	N/A	N/A
Training cost	There is no cost to the health care provider associated with training. However, there may be reduced efficacy, relative to an experienced ENDOCUFF VISION® user, for less experienced clinicians. This has been explored in the model via the learning curve effect whereby there is no improvement in efficacy for the first 20 colonoscopies completed with ENDOCUFF VISION® compared to standard colonoscopy.	See Table C5 and (Marsano et al.)
Other costs – cost of colonoscopy	£547.67 (without identification of polyps) £650.92 (with identification of polyps)	NHS reference costs 2016-17 (NHS Improvement 2017)
Total cost per treatment/patient	£559.72 (without identification of polyps) £662.97 (with identification of polyps)	N/A

Table C7 Costs per treatment/patient associated with the comparator technology in the cost model

Items	Value	Source
Cost of the comparator per treatment/patient	£0	N/A
Consumables (if applicable)	N/A	N/A
Maintenance cost	N/A	N/A
Training cost	N/A	N/A
Other costs – cost of colonoscopy	£547.67 (without identification of polyps) £650.92 (with identification of polyps)	NHS reference costs 2016-17 (NHS Improvement 2017)
Total cost per treatment/patient	£547.67 (without identification of polyps) £650.92 (with identification of polyps)	N/A

Health-state costs

9.3.8 If the cost model presents health states, the costs related to each health state should be presented in table C8. The health states should refer to the states in section 9.1.7. Provide a rationale for the choice of values used in the cost model.

Table C8 reports CRC costs applied in the economic model. These costs were aligned with the validation exercise reported in Section 9.2.5 and cost data were applied from a recently published costing report by NICE (National Institute for Health and Care Excellence 2015).

Table C8 List of health states and associated costs in the economic model

Health states	Items	Value	Reference
CRC (diagnosed during colonoscopy)	Treatment cost	£9,073	Incisive Health 2014 (Incisive Health 2014) weighted by proportion of patients in each stage from Wiegering et al 2016 (Wiegering et al. 2016)
CRC (resulting from symptomatic cancer)	Treatment cost	£10,706	Incisive Health 2014 (Incisive Health 2014) weighted by proportion of patients in each stage from Wiegering et al 2016 (Wiegering et al. 2016)

Costs were also applied to patients undergoing FOBT and to those having a repeat or surveillance colonoscopy. The FOBT costs were determined by outcome: non-compliers (£2.19), normal results (£3.59) and positive result (£12.77). A multiplier of 1.08 was applied to account for people having more than 1 test each. All values were taken and inflated from Whyte et al (Whyte et al. 2012a). Colonoscopy costs are reported in Table C6.

Adverse-event costs

9.3.9 Complete table C9 with details of the costs associated with each adverse event referred to in 9.2.4 included in the cost model. Include all adverse events and complication costs, both during and after longer-term use of the technology.

As discussed in Section 9.2.4, adverse events were not explicitly included in the analysis, however, the proportion of patients having an unsuccessful colonoscopy was included, and these patients would incur the cost of an additional colonoscopy. This is applied as the weighted average of the cost of colonoscopies with and without detection by treatment arm plus the cost of ENDOCUFF VISION® for those patients in that arm.

Miscellaneous costs

9.3.10 Describe any additional costs and cost savings that have not been covered anywhere else (for example, PSS costs, and patient and carer costs). If none, please state.

No other costs were considered as part of the evaluation, however, there may be additional savings from a decline in carer requirements due to reduced colorectal cancer.

9.3.11 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

None were considered relevant to this evaluation.

9.4 Approach to sensitivity analysis

Section 9.4 requires the sponsor to carry out sensitivity analyses to explore uncertainty around the structural assumptions and parameters used in the analysis. All inputs used in the analysis will be estimated with a degree of imprecision. For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

9.4.1 Has the uncertainty around structural assumptions been investigated? State the types of sensitivity analysis that have been carried out in the cost analysis.

Scenario analyses were undertaken to explore uncertainty related to structural assumptions made regarding CRC costs and the learning curve effect. A scenario analysis was undertaken to explore the impact of spreading the cost of CRC treatment costs over the first 2 years after diagnosis rather than the entire cost being applied in the year of diagnosis. In this scenario 50% of the cost was applied in the first year after diagnosis, with the other 50% being applied in the second year after diagnosis. A scenario analysis was also undertaken to explore the impact of excluding the learning curve effect (see Table C6 for explanation of learning curve effect).

Extensive sensitivity analysis was also performed around parameter uncertainty as described in Section 9.4.2.

9.4.2 Was a deterministic and/or probabilistic sensitivity analysis undertaken? If not, why not? How were variables varied and what was the rationale for this? If relevant, the distributions and their sources should be clearly stated.

Both deterministic and probabilistic sensitivity analysis were undertaken.

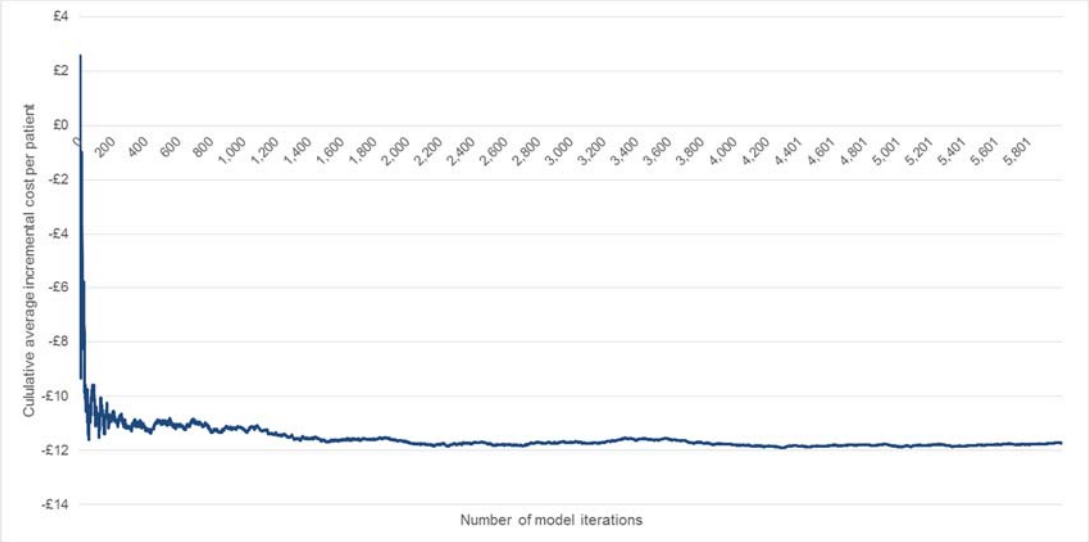
In deterministic sensitivity analysis individual input parameters were varied to assess the impact on the results of the model and identify any key drivers. Where the direction of results changed during the analysis, threshold values have been reported. These threshold values indicate the lowest/highest value that a particular input parameter takes for the incremental costs to be cost neutral.

Several scenario analyses were undertaken to explore the impact of changing one or more specific input parameters. These are detailed in Tables C10.2. and C10.2b. Scenarios around the difference in ADR between ENDOCUFF VISION® and standard colonoscopy were undertaken inputting the lower and upper bounds of confidence intervals reported by Ngu et al.(Ngu et al. 2018b). The ADR with standard colonoscopy was kept constant and the ADR with ENDOCUFF VISION® was varied by the specified amount. For the higher confidence interval, the ADR with ENDOCUFF VISION® was increased to 100% minus the PDR. Where the direction of results changed during the analysis, threshold values have been reported. Scenarios were also conducted around alternative sources for the cost of CRC treatment (as reported in Section 9.3.3), and as discussed in Section 9.4.1, around spreading the cost of CRC over the first two years after diagnosis and the learning curve effect.

Ranges have, where possible, been taken from the literature. Where not available, clinical opinion or conservative assumptions were used (See table C10.1 and C10.3)

Probabilistic sensitivity analysis was performed using 2,000 model iterations. This was the number of iterations required to achieve stability, as shown in Figure C5. A probabilistic scenario analysis was also run where the proportion of detected adenoma patients falling into each risk category were varied. This is discussed in further detail in Section 9.4.4.

Figure C5: PSA model iterations



9.4.3 Complete table C10.1, C10.2 and/or C10.3 as appropriate to summarise the variables used in the sensitivity analysis.

Table C10.1 Variables used in one-way scenario-based deterministic sensitivity analysis

Variable	Base-case value	Range of values	Explanation of range used
Starting age	62	55 to 74	Bowel cancer screening age range (Bowel Cancer UK 2017)
Proportion of men	57%	0% to 100%	Wide range assumed
Years between colonoscopy for high risk patients	1	1 to 3	Wide range assumed
Years between colonoscopy for low risk patients	5	3 to 9	Wide range assumed
Proportion of successful colonoscopies: ENDOCUFF VISION®	97.7%	78.2% to 100%	+/- 20%
Proportion of successful colonoscopies: Standard colonoscopy	97.8%	78.2% to 100%	+/- 20%
Probability of adenoma recurrence given history of low risk adenoma (year 1)	18.0%	14.4% to 21.6%	+/- 20%
Probability of adenoma recurrence given history of low risk adenoma (year 2+)	5.0%	4% to 6%	+/- 20%
Probability of adenoma recurrence given history	25.0%	20% to 30%	+/- 20%

Variable	Base-case value	Range of values	Explanation of range used
of high risk adenoma (year 1)			
Probability of adenoma recurrence given history of high risk adenoma (year 2+)	6.0%	4.8% to 7.2%	+/- 20%
Annual transition: Normal epithelium to low risk adenoma	2.0%	1.6% to 2.4%	+/- 20%
Annual transition: Low risk adenoma to high risk adenoma	0.8%	0.6% to 1.0%	+/- 20%
Annual transition: High risk adenoma to CRC (55-59 years)	2.6%	2.1% to 3.1%	+/- 20%
Annual transition: High risk adenoma to CRC (60-64 years)	3.2%	2.6% to 3.9%	+/- 20%
Annual transition: High risk adenoma to CRC (65-69 years)	4.1%	3.3% to 5.0%	+/- 20%
Annual transition: High risk adenoma to CRC (70-74 years)	4.5%	3.6% to 5.3%	+/- 20%
Annual transition: High risk adenoma to CRC (75-79 years)	5.1%	4.0% to 6.1%	+/- 20%
Annual transition: High risk adenoma to CRC (80-84 years)	5.3%	4.3% to 6.4%	+/- 20%
ADR: ENDOCUFF VISION®	61.7%	51% to 73%	+/- 20%
ADR: Standard colonoscopy	50.9%	41% to 61%	+/- 20%
Cost of diagnostic colonoscopy: ENDOCUFF VISION®	£548	£424 to £627	Lower to upper quartile ranges used (NHS Improvement 2017)
Additional cost of therapeutic colonoscopy: ENDOCUFF VISION®	£103.25	£83 to £124	+/- 20%
Cost of diagnostic colonoscopy: Standard colonoscopy	£548	£424 to £627	Lower to upper quartile ranges used (NHS Improvement 2017)
Additional cost of therapeutic colonoscopy: Standard colonoscopy	£103.25	£83 to £124	+/- 20%
Cost of CRC treatment – identified via colonoscopy	£9,073	£5,188 to £20,148	Lowest and highest ranges used from all cancer treatment cost sources
Additional cost of CRC treatment resulting from missed lesions	£1,633	£833 to £4,775	Lowest and highest ranges used from all

Variable	Base-case value	Range of values	Explanation of range used
			cancer treatment cost sources
Number of training colonoscopies	126	101 to 151	+/- 20%
Compliance with surveillance colonoscopy	83.0%	66% to 100%	+/- 20%
Compliance with FOBT screening	85.0%	68% to 100%	+/- 20%
Compliance with colonoscopy following FOBT screening	79.0%	63% to 95%	+/- 20%
Probability of requiring a colonoscopy: normal	0.5%	0.4% to 0.6%	+/- 20%
Probability of requiring a colonoscopy: low risk adenoma	1.0%	0.8% to 1.2%	+/- 20%
Probability of requiring a colonoscopy: high risk adenoma	6.5%	5.2% to 7.8%	+/- 20%
Cost of FOBT: non-compliers	£2.19	£1.75 to £2.63	+/- 20%
Cost of FOBT: normal result (with multiplier)	£3.88	£3.10 to £4.66	+/- 20%
Cost of FOBT: positive result (with multiplier)	£13.80	£11.04 to £16.56	+/- 20%
Proportion of patients CRC detected through screening - Stage 1	31%	19% to 41%	Wide range assumed using multiplier
Proportion of patients CRC detected through screening - Stage 2	30%	18% to 39%	Wide range assumed using multiplier
Proportion of patients CRC detected through screening - Stage 3	28%	17% to 37%	Wide range assumed using multiplier
Proportion of patients CRC detected through screening - Stage 4	10%	5% to 15%	Wide range assumed using multiplier
Proportion of patients CRC missed at screening - Stage 1	18%	10% to 25%	Wide range assumed using multiplier
Proportion of patients CRC missed at screening - Stage 2	32%	19% to 41%	Wide range assumed using multiplier
Proportion of patients CRC missed at screening - Stage 3	23%	13% to 31%	Wide range assumed using multiplier
Proportion of patients CRC missed at screening - Stage 4	27%	15% to 35%	Wide range assumed using multiplier

Table C10.2 Variables used in scenario-based sensitivity analysis

Variable	Difference in ADR	Cost of CRC treatment – patients identified through colonoscopy	Cost of CRC treatment – patients developing CRC from missed detection	Number of training colonoscopies (in year 1 and subsequent years)	Proportion of CRC costs applied in year of diagnosis (remainder applied in following year)
Base case	10.81%	£9,073	£10,706	126	100%
Scenario 1: Difference in ADR lower confidence interval	5.1%				
Scenario 2: Difference in ADR upper confidence interval	36.9%				
Scenario 3: Removal of learning curve effect				0	
Scenario 4: Spreading CRC treatment costs					50%

Table C10.2b Variables used in colorectal cancer treatment cost scenario-based sensitivity analysis

Colorectal cancer cost source	Weighting of stages source – Wiegering et al 2016 (Wiegering et al. 2016)		Weighting of stages alternative source – Toes-Zoutendijk et al 2017 (Toes-Zoutendijk et al. 2017)	
	Colorectal cancer cost - Screening	Colorectal cancer cost - Symptomatic	Colorectal cancer cost - Screening	Colorectal cancer cost - Symptomatic
Incisive health (Incisive Health 2014)	£9,073	£10,706	£7,971	£11,234
EEPRU (Whyte et al. 2012b)	£5,392	£6,240	£5,188	£6,468
Lee (Lee 2010)	£15,595	£16,838	£14,353	£17,917
NICE - NG12 (National Institute for Health and Care Excellence 2015)	£14,753	£15,924	£13,594	£17,015
Public Health England (Public Health England 2016)	£7,563	£9,468	£6,630	£9,756
NICE - CG118 (National Institute for Health and Care Excellence 2011a)	£18,005	£20,405	£16,786	£20,995
Dept. of Health (Department of Health 2011)	£15,811	£16,644	£14,817	£17,711
Westwood (Westwood et al. 2017)	£18,967	£20,280	£17,490	£21,669
Whyte (Whyte et al. 2012a)	£20,148	£22,715	£18,748	£23,523
Picot (Picot et al. 2017) (NICE report for virtual chromoendoscopy)	£5,397	£6,245	£5,192	£6,473
Murphy (Murphy et al. 2017)	£20,018	£22,573	£18,627	£23,376

Table C10.3 Variable values used in probabilistic sensitivity analysis

Variable	Base-case value	Distribution	Explanation of range used
Effectiveness			
Proportion of successful colonoscopies: ENDOCUFF VISION®	97.7%	Beta SE: 0.008	SE calculated from alpha and beta values which were taken from Ngu et al 2018 (Ngu et al. 2018b)
Proportion of successful colonoscopies: Standard colonoscopy	97.8%	Beta SE: 0.007	SE calculated from alpha and beta values which were taken from Ngu et al 2018 (Ngu et al. 2018b)
Polyp detection rate: ENDOCUFF VISION®	12.2%	Beta SE: 0.016	SE calculated from alpha and beta values which were taken from Ngu et al 2018 (Ngu et al. 2018b)
Polyp detection rate: Standard colonoscopy	12.4%	Beta SE: 0.016	SE calculated from alpha and beta values which were taken from Ngu et al 2018 (Ngu et al. 2018b)
Difference in ADR	10.8%	Gamma CI: 5.1% to 36.9%	Upper and lower confidence intervals from Ngu et al 2018 (Ngu et al. 2018b) with upper confidence interval adjusted so that ADR+PDR does not exceed 100%. Not varied in PSA scenario analysis.
Annual transitions			
Normal epithelium to low risk adenoma	2.0%	Lognormal CI: 1.9% to 2.1%	Whyte et al 2012 (Whyte et al. 2012a)
Low risk adenoma to high risk adenoma	0.8%	Lognormal CI: 0.6% to 0.8%	Whyte et al 2012 (Whyte et al. 2012a)
High risk adenoma to CRC (55-59)	2.6%	Lognormal CI: 2.0% to 3.1%	Assumption
High risk adenoma to CRC (60-64)	3.2%	Lognormal CI: 2.5% to 3.9%	Assumption
High risk adenoma to CRC (65-69)	4.1%	Lognormal CI: 3.5% to 4.7%	Assumption
High risk adenoma to CRC (70-74)	4.5%	Lognormal CI: 4.0% to 4.8%	Assumption
High risk adenoma to CRC (74-79)	5.1%	Lognormal CI: 4.5% to 5.5%	Assumption
High risk adenoma to CRC (80-84)	5.3%	Lognormal CI: 4.8% to 5.8%	Assumption
Mortality rate for CRC	20.8%	Lognormal CI: 19.3% to 22.8%	Assumption based on McPhail et al 2015 (McPhail et al. 2015) (overstated confidence intervals)
Adenoma recurrence given history of low risk adenoma (year 1)	18.0%	Lognormal CI: 17% to 19%	Assumption

Variable	Base-case value	Distribution	Explanation of range used
Adenoma recurrence given history of low risk adenoma (year 2+)	5.0%	Lognormal CI: 4.5% to 5.5%	Assumption
Adenoma recurrence given history of high risk adenoma (year 1)	25.0%	Lognormal CI: 23% to 27%	Assumption
Adenoma recurrence given history of high risk adenoma (year 2+)	6.0%	Lognormal CI: 5.5% to 6.5%	Assumption
Proportion of detected adenoma patients: No adenoma detected (ECV)	38.3%	Dirichlet SE: 0.024	Ngu et al 2018 (Ngu et al. 2018b). Only varied in PSA scenario analysis.
Proportion of detected adenoma patients: Low risk (ECV)	34.5%	Dirichlet SE: 0.024	Ngu et al 2018 (Ngu et al. 2018b). Only varied in PSA scenario analysis.
Proportion of detected adenoma patients: High risk (ECV)	20.6%	Dirichlet SE: 0.020	Ngu et al 2018 (Ngu et al. 2018b). Only varied in PSA scenario analysis.
Proportion of detected adenoma patients: Carcinoma (ECV)	6.6%	Dirichlet SE: 0.012	Ngu et al 2018 (Ngu et al. 2018b). Only varied in PSA scenario analysis.
Proportion of detected adenoma patients: No adenoma detected (SC)	49.1%	Dirichlet SE: 0.025	Ngu et al 2018 (Ngu et al. 2018b). Only varied in PSA scenario analysis.
Proportion of detected adenoma patients: Low risk (SC)	27.8%	Dirichlet SE: 0.022	Ngu et al 2018 (Ngu et al. 2018b). Only varied in PSA scenario analysis.
Proportion of detected adenoma patients: High risk (SC)	19.4%	Dirichlet SE: 0.020	Ngu et al 2018 (Ngu et al. 2018b). Only varied in PSA scenario analysis.
Proportion of detected adenoma patients: Carcinoma (SC)	3.7%	Dirichlet SE: 0.009	Ngu et al 2018 (Ngu et al. 2018b). Only varied in PSA scenario analysis.
Costs			
Cost of diagnostic colonoscopy: ENDOCUFF VISION®	£547.67	Gamma SE: £109.53	Assumption
Additional cost of therapeutic colonoscopy: ENDOCUFF VISION®	£103.25	Gamma SE: £20.65	Assumption
Cost of diagnostic colonoscopy: Standard colonoscopy	£547.67	Gamma SE: £109.53	Assumption
Additional cost of therapeutic colonoscopy: Standard colonoscopy	£103.25	Gamma SE: £20.65	Assumption

Variable	Base-case value	Distribution	Explanation of range used
Cost of colorectal cancer - identified through colonoscopy	£9,073	Gamma SE: £1,814.66	Assumption
Additional cost of colorectal cancer - resulting from missed adenoma	£1,633	Gamma SE: £326.54	Assumption
FOBT			
Probability of requiring a colonoscopy: normal	0.5%	Beta SE: 0.021	Assumption
Probability of requiring a colonoscopy: low risk adenoma	1.0%	Beta SE: 0.030	Assumption
Probability of requiring a colonoscopy: high risk adenoma	6.5%	Beta SE: 0.074	Assumption
Cost of FOBT: non-compliers	£2.19	Gamma SE: £0.44	Assumption
Cost of FOBT: normal result (with multiplier)	£3.88	Gamma SE: £0.78	Assumption
Cost of FOBT: positive result (with multiplier)	£13.80	Gamma SE: £2.76	Assumption

9.4.4 If any parameters or variables listed in section 9.2.6 were omitted from the sensitivity analysis, provide the rationale.

The following parameters were not varied as they were considered to be unlikely to change or constant:

- Discount rates
- Cost of ENDOCUFF VISION®
- Age related mortality
- Number of patients in model (hypothetical and has no effect on per patient results)

The proportion of detected and undetected adenoma by risk type was not varied as part of the base case sensitivity analysis. In the base case the distribution of undetected adenoma by risk type in the ENDOCUFF VISION® arm is assumed to be equal to the detected adenoma as data reporting on the spread of undetected adenoma cannot be generated. These figures are then used to calculate the spread of undetected adenoma by risk type in the standard colonoscopy arm assuming that overall there are the same number

of low risk adenoma, high risk adenoma and carcinoma patients in each of the treatment arms (i.e. detected plus undetected will be equal between arms). It was not possible to vary the spread of detected or undetected adenoma by risk type without building in specific scenarios which would require making further assumptions. Allowing the numbers to vary without restriction resulted in a number of implausible scenarios where the number of some risk types of undetected adenoma became negative, which whilst mathematically possible is not clinically plausible. A PSA exploratory scenario was run with specific scenarios built in to prevent clinically implausible outcomes. Specifically, where the proportion of patients with detected adenoma in any of the risk groups with standard colonoscopy was higher than with ENDOCUFF VISION®, adjustments were made to prevent this from happening. This occurred because the sensitivity of colonoscopy with or without ENDOCUFF VISION® was assumed to be 100% for the comparator with the highest ADR. This meant, in some instances of the PSA, in order to maintain the same total number of each type of adenoma across treatment arms (low risk, high risk, CRC) the number of undetected adenoma were negative. To prevent this happening, patients were reassigned to a "worse" classification of adenoma, i.e. implying that they had been miss classified (e.g. had a low risk adenoma identified but a high risk adenoma missed).

9.5 Results of de novo cost analysis

Section 9.5 requires the sponsor to report the de novo cost analysis results. These should include the following:

- costs
- disaggregated results such as costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment
- a tabulation of the mean cost results
- results of the sensitivity analysis.

Base-case analysis

9.5.1 Report the total costs associated with use of the technology and the comparator(s) in the base-case analysis. A suggested format is presented in table C11.

Table C11 Base-case results

	Total per patient cost (£)
Colonoscopy with ENDOCUFF VISION®	£1,532
Standard colonoscopy	£1,544

9.5.2 Report the total difference in costs between the technology and comparator(s).

Total savings per patient = £11.59

9.5.3 Provide details of the costs for the technology and its comparator by category of cost. A suggested format is presented in table C12.

Table C12 Summary of costs by category of cost per patient

Item	Cost - ENDOCUFF VISION®	Cost - Standard care	Increment	Absolute increment	% absolute increment
Cost of colonoscopy without detection*	£307	£344	-£38	£38	19%
Cost of colonoscopy with detection*	£600	£505	£96	£96	47%
Cost of colorectal cancer treatment	£619	£688	-£69	£69	34%
FOBT costs	£7	£8	-£1	£1	0%
Total	£1,532	£1,544	-£12	£230	100%
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee *Cost of the technology is included as an addition to the cost of a colonoscopy					

9.5.4 If appropriate, provide details of the costs for the technology and its comparator by health state. A suggested format is presented in table C13.

Not applicable. Costs included for health states are shown in Table C12.

9.5.5 If appropriate, provide details of the costs for the technology and its comparator by adverse event. A suggested format is provided in table C14.

Not applicable. As discussed in Section 9.2.4 adverse events were not explicitly modelled.

Sensitivity analysis results

9.5.6 Present results of deterministic one-way sensitivity analysis of the variables described in table C10.1.

The result of the deterministic sensitivity analysis is presented in Figure C.6 below. All parameters were included in the sensitivity analysis as described in Table C10.1, however only the top 20 influencing parameters are shown on the diagram for clarity. Threshold values, i.e. values where the results change direction, for the main cost drivers are presented in Table C15.

Figure C.6: Tornado diagram showing univariate sensitivity analysis

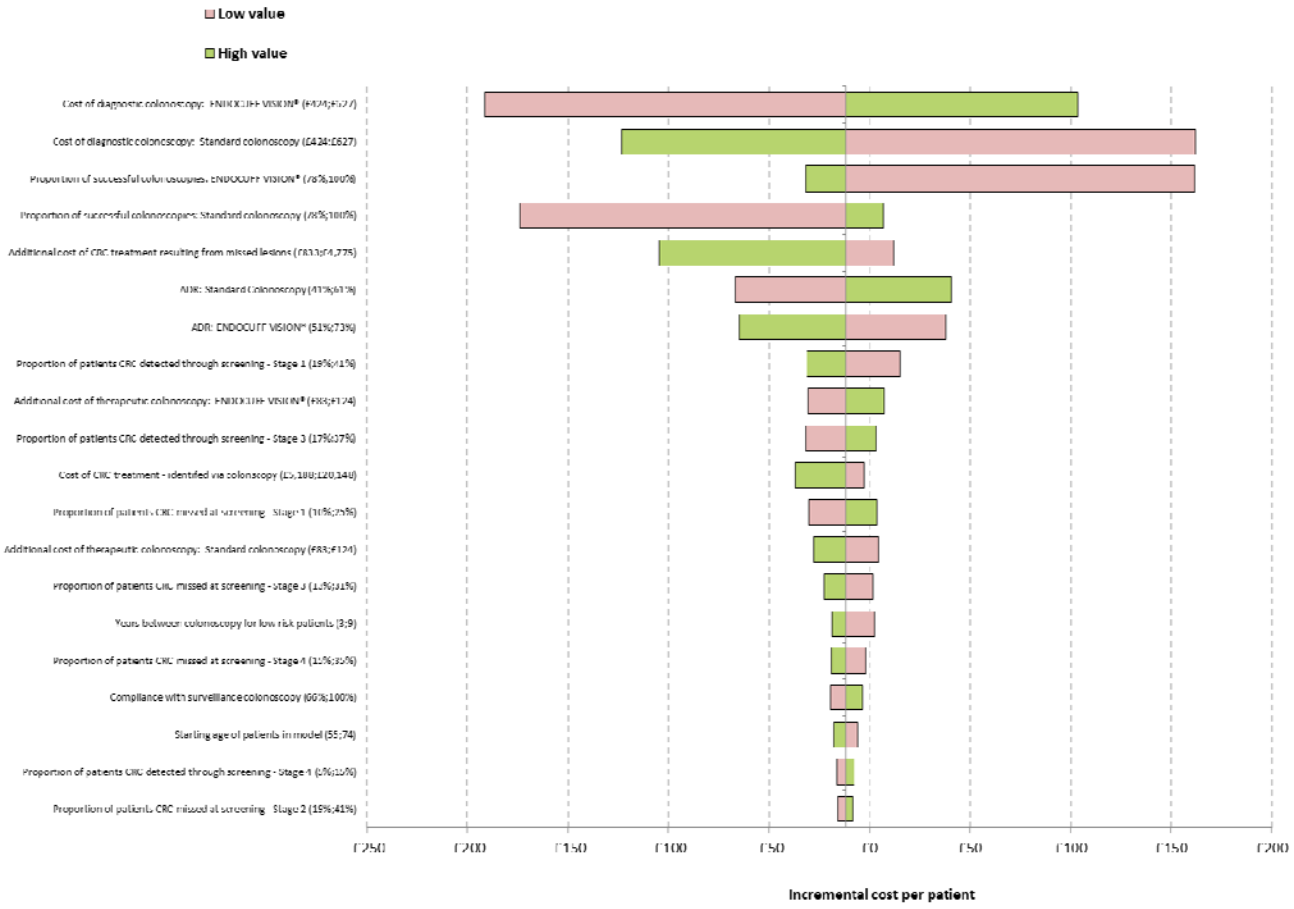


Table C15: Threshold values for main cost drivers (deterministic)

Parameter	Base case	Threshold value	Plausibility
Improvement in ADR with ENDOCUFF VISION®	10.81%	8.35%%	Falls between confidence intervals reported by Ngu et al 2018 [5.1% to ∞] so is considered to be plausible. However, this confidence interval was used in the PSA and therefore the uncertainty for this parameter is captured within the PSA and results remained cost saving for the majority of iterations. Results of the PSA are presented in Section 9.5.8.
Additional cost of colorectal cancer treatment resulting from missed lesions	£1,633	£1,241	Falls within ranges identified from alternative sources so considered to be plausible. However, this is dependent on the cost of colorectal cancer for patients identified through colonoscopy.
Cost of diagnostic colonoscopy (ENDOCUFF VISION®)	£548	£569	Not considered to be very uncertain as obtained from nationally published source. Additionally it is unlikely that the cost of diagnostic colonoscopy with ENDOCUFF VISION® would vary independently from cost of standard diagnostic colonoscopy as colonoscopy with ENDOCUFF VISION® has been shown to have equivalent insertion and withdrawal times (Ngu et al. 2018b). If varied together cost of diagnostic colonoscopy would have to fall by more than £140.
Cost of diagnostic colonoscopy (Standard care)	£548	£529	Not considered to be very uncertain as obtained from nationally published source. Additionally it is unlikely that the cost of diagnostic colonoscopy with ENDOCUFF VISION® would vary independently from cost of standard diagnostic colonoscopy as colonoscopy with ENDOCUFF VISION® has been shown to have equivalent insertion and withdrawal times (Ngu et al. 2018b). If varied together cost of diagnostic colonoscopy would have to fall by more than £140.
Proportion of successful colonoscopies (ENDOCUFF VISION®)	97.7%	96.4%	Within the confidence interval reported by Ngu et al. so is considered to be plausible.
Proportion of successful colonoscopies	97.8%	99.2%	Within the confidence interval reported by Ngu et al. so is considered to be plausible.

(Standard colonoscopy)			
Additional cost of therapeutic colonoscopy (ENDOCUFF VISION®)	£651	£664	Not considered to be very uncertain as obtained from nationally published source. Additionally it is unlikely that the cost of therapeutic colonoscopy with ENDOCUFF VISION® would vary independently from cost of standard therapeutic colonoscopy as colonoscopy with ENDOCUFF VISION® has been shown to have equivalent insertion and withdrawal times (Ngu et al. 2018b). If varied together cost of therapeutic colonoscopy would have to increase by more than £110.
Additional cost of therapeutic colonoscopy (Standard colonoscopy)	£651	£637	Not considered to be very uncertain as obtained from nationally published source. Additionally it is unlikely that the cost of therapeutic colonoscopy with ENDOCUFF VISION® would vary independently from cost of standard therapeutic colonoscopy as colonoscopy with ENDOCUFF VISION® has been shown to have equivalent insertion and withdrawal times (Ngu et al. 2018b). If varied together cost of therapeutic colonoscopy would have to increase by more than £110.
Years between colonoscopy for low risk patients	5 years	3 years	Based on NICE clinical guideline CG118 so considered to be not plausible.

9.5.7 Present results of deterministic multi-way scenario sensitivity analysis described in table C10.2.

Within this section the following results are presented:

- Results of the model using CRC staging data from England reported by Sagar et al. For this scenario, deterministic and probabilistic results as well as a tornado diagram are presented (Sagar et al. 2015).
- Results of the deterministic multi-way scenario sensitivity analyses in Tables C16b and C16c.

The results of the model using the data from Sagar et al. are reported in Table C16a. A cost saving of £56 per patient is estimated.

Table C16a: Results of model using English data reporting on CRC breakdown (Sagar et al. 2015)

Item	Cost - ENDOCUFF VISION®	Cost - Standard care	Increment
Deterministic results			
Cost of colonoscopy without detection*	£307	£344	-£38
Cost of colonoscopy with detection*	£600	£505	£96
Cost of colorectal cancer treatment	£547	£660	-£113
FOBT costs	£7	£8	-£1
Total	£1,461	£1,516	-£56
Probabilistic results			
Probabilistic incremental cost			-£56
Proportion of iterations in which ENDOCUFF VISION® is cost saving			99.4%

Table C16b: Results of deterministic multi-way scenario sensitivity analysis

Scenario	*Total cost per patient with ENDOCUFF VISION®*	*Total cost per patient with Standard colonoscopy*	*Incremental cost per patient*
Base case	£1,532	£1,544	-£11.59
Scenario 1: Difference in ADR lower confidence interval	£1,444	£1,429	£15.21
Scenario 2: Difference in ADR upper confidence interval	£1,937	£2,077	-£139.47
Scenario 3: Removal of learning curve effect	£1,525	£1,544	-£18.81
Scenario 4: Spreading CRC treatment costs	£1,521	£1,530	-£9.16

Table C16c: Results of deterministic colorectal cancer costs multi-way scenario sensitivity analysis

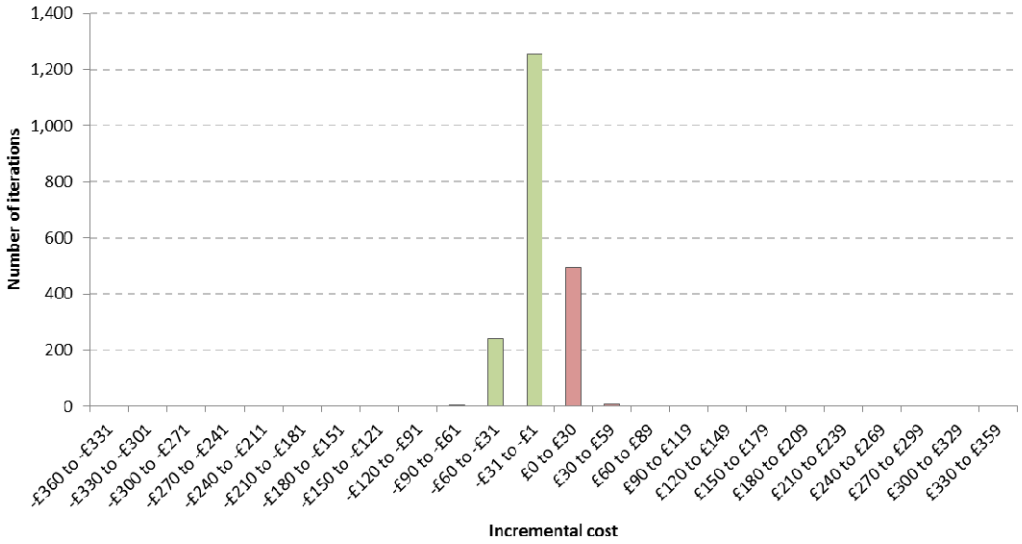
Colorectal cancer cost source	Weighting of stages source – Wiegering et al 2016 (Wiegering et al. 2016) [Basecase]		Incremental cost per patient	Weighting of stages source – Sagar et al 2015 (Sagar et al. 2015)		Incremental cost per patient	Weighting of stages alternative source – Toes-Zoutendijk et al 2017 (Toes-Zoutendijk et al. 2017)		Incremental cost per patient
	CRC cost - Screening	CRC cost - Symptomatic		CRC cost - Screening	CRC cost - Symptomatic		CRC cost - Screening	CRC cost - Symptomatic	
Incisive health (Incisive Health 2014) [Basecase]	**£9,073**	**£10,706**	**-£11.59**	£7,937	£11,144	**-£55.58**	£7,971	£11,234	**-£57.34**
EEPRU (Whyte et al. 2012b)	£5,392	£6,240	**£19.97**	£5,118	£6,402	**£7.71**	£5,188	£6,468	**£7.65**
Lee (Lee 2010)	£15,595	£16,838	**-£14.87**	£14,320	£17,973	**-£83.27**	£14,353	£17,917	**-£80.71**
NICE - NG12 (National Institute for Health and Care Excellence 2015)	£14,753	£15,924	**-£10.83**	£13,540	£17,063	**-£77.66**	£13,594	£17,015	**-£74.78**

Public Health England (Public Health England 2016)	£7,563	£9,468	**-£16.22**	£6,492	£9,478	**-£45.79**	£6,630	£9,756	**-£50.24**
NICE - CG118 (National Institute for Health and Care Excellence 2011a)	£18,005	£20,405	**-£54.58**	£16,466	£20,501	**-£99.43**	£16,786	£20,995	**-£105.31**
Dept. of Health (Department of Health 2011)	£15,811	£16,644	**-£3.23**	£14,826	£17,866	**-£66.29**	£14,817	£17,711	**-£61.95**
Westwood (Westwood et al. 2017)	£18,967	£20,280	**-£24.60**	£17,421	£21,730	**-£109.71**	£17,490	£21,669	**-£106.04**
Whyte (Whyte et al. 2012a)	£20,148	£22,715	**-£64.37**	£18,362	£22,973	**-£120.78**	£18,748	£23,523	**-£126.50**
Picot (Picot et al. 2017) (NICE report for virtual chromoendoscopy)	£5,397	£6,245	**£19.96**	£5,123	£6,407	**£7.69**	£5,192	£6,473	**£7.63**
Murphy (Murphy et al. 2017)	£20,018	£22,573	**-£63.72**	£18,243	£22,829	**-£119.77**	£18,627	£23,376	**-£125.46**

9.5.8 Present results of the probabilistic sensitivity analysis described in table C10.3.

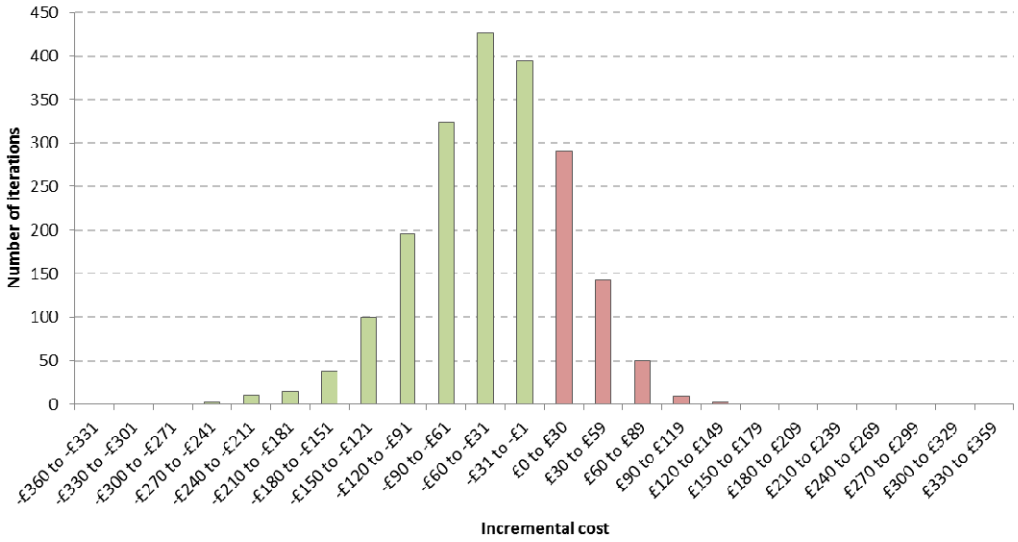
Probabilistic sensitivity analysis was conducted based on 2,000 iterations. ENDOCUFF VISION® was cost saving in 77.4% of iterations and the average probabilistic cost savings were £11.76 per patient. Figure C.7a shows the distribution of these results.

Figure C.7a: Probabilistic results – Base case scenario



The PSA scenario where the risk groups for patients with detected adenoma were varied was also run using 2,000 iterations. This produced a wider variation in incremental costs and ENDOCUFF VISION® was cost saving in 77.3% of iterations and the average probabilistic cost savings were £41.53 per patient.

Figure C7b: Probabilistic results – Risk groups scenario



9.5.9 What were the main findings of each of the sensitivity analyses?

Deterministic and scenario analyses

The results of the deterministic sensitivity analyses show that the model is sensitive to changes in a number of key parameters including the improvement in ADR with ENDOCUFF VISION®, colorectal cancer treatment costs, costs of colonoscopy, the proportion of colonoscopies that are successful, and the risk surveillance strategy for low risk patients.

Should the improvement in ADR with ENDOCUFF VISION® fall below 8.35%, ENDOCUFF VISION® is no longer cost saving. This falls within the confidence intervals reported by Ngu et al 2018 and is therefore plausible. However, this parameter would also likely be affected by the baseline ADR with standard colonoscopy, i.e. a lower baseline ADR may increase scope for improvement and vice versa, and may therefore vary across settings. Other real world studies identified in the clinical review showed similar baseline rates of ADR with standard colonoscopy (52%, 55%) and also demonstrated a significant improvement with ENDOCUFF VISION® (16%, 28%) (Tsiamoulos et al., Rameshshanker et al. 2016).

The model is sensitive to the data source used for breakdown of stage for symptomatic and screen detected CRC. In the base case, cost savings with ENDOCUFF VISION® were generated using German data (Wiegering et al. 2016). Where alternative English data were used these cost savings increased. This occurred due to a larger benefit in screen detected cancer (i.e. earlier stage of detection) being demonstrated in the English data (Sagar et al. 2015). These data are somewhat limited in that the patients within this study (particularly for symptom detected cancer) are older than those patients enrolled in the ADENOMA study. Within the model, it is assumed that patients with missed carcinoma become symptomatic and incur costs within a year. The use of the English data suggests that these patients may take longer than a year to become symptomatic and therefore the net present value of their CRC costs would be lower than those within the model (i.e. they may occur further into the future and should be discounted accordingly).

Colorectal cancer treatment costs are uncertain due to wide variation identified in the literature. However, a number of different sources were identified and tested in the model and ENDOCUFF VISION® remained cost saving across the majority (see Table C16b). This input was also verified with clinical key opinion leaders (KOLs) and is consistent with costing applied in NICE guideline development (National Institute for Health and Care Excellence 2015). Analysis spreading colorectal cancer treatment costs over the first 2 years in the model, rather than patients incurring all treatment costs in the year of diagnosis, indicated ENDOCUFF VISION® would remain cost-saving, although the magnitude of this saving would be reduced.

Costs of colonoscopy, although a key driver in the model, are published in NHS reference costs and therefore are not considered to be very uncertain. Further it is unlikely that in the real world, the cost of a colonoscopy with ENDOCUFF VISION® would differ largely from the cost of a standard colonoscopy (excluding the cost of the device) as evidence has shown the duration of colonoscopy is unlikely to vary substantially (Ngu et al. 2018b). When varied together, the cost of a diagnostic colonoscopy would have to fall by more than £140 or the cost of a

therapeutic colonoscopy would have to increase by over £110 for the results to become cost increasing.

The proportion of successful colonoscopies in both the standard colonoscopy arm and the ENDOCUFF VISION® arm varying can impact on the potential cost savings of ENDOCUFF VISION®. Ngu et al report a difference between arms of 0.1%, which considers ENDOCUFF VISION® to be non-inferior to standard colonoscopy. However, varying the difference in the model by the lower bound of the confidence interval (-2.1%) reported by Ngu et al. results in a cost increasing result of £6.52 (assuming caecal intubation rate with standard colonoscopy remains at 97.8%).

The risk surveillance strategy for a repeat colonoscopy for low risk patients' would have to reduce to 3 years for ENDOCUFF VISION® to become cost increasing (compared with 5 years in the base case). This risk strategy is based on NICE clinical guideline CG118 and is therefore considered to be unlikely to change to this extent.

Scenario analysis conducted around the learning curve effect showed this parameter to have minimal impact on the results.

Probabilistic sensitivity analysis

Probabilistic sensitivity analysis demonstrated that the base case results were fairly robust to joint input parameter uncertainty with over 75% of model iterations found to be cost-saving. However, not all parameters could be varied due to paucity of data which limits the results of the PSA. Specifically the risk type of detected and undetected adenomas could not be varied. This is discussed in more detail in Section 9.4.4. A scenario was run for the PSA to explore the effect of varying these risk types on the uncertainty in the model. The results of this scenario demonstrated that this had very little effect on the probability of ENDOCUFF VISION® being cost saving. However, the average probabilistic cost saving was increased due to a wider variation in average incremental costs, and an increase in the number of missed adenomas in the standard care arm.

9.5.10 What are the key drivers of the cost results?

The key drivers in the model are the following:

(i) Cost of colorectal cancer treatment resulting from missed lesions

(ii) Cost of colorectal cancer treatment identified via colonoscopy

(iii) Proportion of patients by stage of cancer identified via colonoscopy or due to missed lesions (stages 1 and 3)

(iv) ADR with ENDOCUFF VISION® and standard colonoscopy

(v) Cost of diagnostic colonoscopy (both ENDOCUFF VISION® and standard colonoscopy)

(vi) Proportion of successful colonoscopies (both ENDOCUFF VISION® and standard colonoscopy)

(vii) Additional cost of therapeutic colonoscopy (both ENDOCUFF VISION® and standard colonoscopy)

(viii) Years between colonoscopy for low risk patients

Miscellaneous results

9.5.11 Describe any additional results that have not been specifically requested in this template. If none, please state.

Additional results	ENDOCUFF VISION®	Standard colonoscopy	Incremental	Explanation
Colorectal cancer deaths per patient	0.014	0.015	-0.001	Decrease of 0.001 colorectal cancer deaths with ENDOCUFF VISION®. This is *not* captured within the costs in the model.
Number of patients with detected adenoma	680	578	102	Increase of 102 additional patients with adenoma detected with ENDOCUFF VISION®®. This is already captured within costs in the model.
Number of patients with	163	160	2	Increase of 2 additional patients with detected

detected polyps (and no adenoma)				polyps with ENDOCUFF VISION®®. This is already captured within costs in the model.
Total number of complete colonoscopies	1,476	1,421	56	Increase of 56 additional colonoscopies with ENDOCUFF VISION® i.e. due to increase in surveillance colonoscopies because more adenoma detected. This is already captured within the costs in the model.
Cases of colorectal cancer per patient	0.068	0.071	-0.003	Decrease of 0.003 cases of colorectal cancer with ENDOCUFF VISION®. This is already captured within the costs in the model.
Incremental cost per colorectal cancer death avoided	-	-	Dominant	Incremental cost per colorectal cancer death avoided is dominant. i.e. ENDOCUFF VISION® reduces the number of colorectal cancer deaths at no additional cost.

9.6 Subgroup analysis

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. Sponsors are required to complete section 9.6 in accordance with the subgroups identified in the scope and for any additional subgroups considered relevant.

Types of subgroups that are not considered relevant are those based solely on the following factors.

- Subgroups based solely on differential treatment costs for individuals according to their social characteristics.
- Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, if the costs of facilities available for providing the technology vary according to location).

9.6.1 Specify whether analysis of subgroups was undertaken and how these subgroups were identified. Cross-reference the response to the decision problem in table A1 and sections 3.2 and 7.4.4.

Cost-consequence analysis was only undertaken for the screening subgroup.

9.6.2 Define the characteristics of patients in the subgroup(s).

Not applicable.

9.6.3 Describe how the subgroups were included in the cost analysis.

Not applicable.

9.6.4 What were the results of the subgroup analysis/analyses, if conducted? The results should be presented in a table similar to that in section 9.5.1 (base-case analysis).

Not applicable.

9.6.5 Were any subgroups not included in the submission? If so, which ones, and why were they not considered?

The symptomatic population i.e. those undergoing colonoscopy due to referral for symptoms, were not considered in the economic model because ENDOCUFF VISION® has not yet been demonstrated to be more effective than standard colonoscopy in this population and therefore would not be cost saving. This is described in Section 9.1.2.

9.7 Validation

9.7.1 Describe the methods used to validate and cross-validate (for example with external evidence sources) and quality-assure the model. Provide

references to the results produced and cross-reference to evidence identified in the clinical and resources sections.

The economic model was built in Microsoft Excel by one health economist, and checked for errors by a second health economist independent of the project. The model structure and model input parameters were validated by clinical experts as described in Sections 9.2.5 and 9.3.4. In summary, both the model structure and cost inputs were considered valid. Additional confidence in the face validity of the model is taken from the use of the same structure as applied in evaluations of the BCSP. Finally, the costs applied in the model are aligned with recent NICE costing guidance.

The model results were cross-validated against the published cost-effectiveness analyses identified in the economic literature search. The model found ENDOCUFF VISION® to be cost saving in line with the published evidence (Section 9.8.2). However, this evidence is limited to1 study undertaken from a German perspective.

9.8 Interpretation of economic evidence

9.8.1 Are the results from this cost analysis consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

One cost analysis on ENDOCUFF VISION® in a German healthcare setting was identified in the economic literature search (Conway et al. 2015). Conway et al. reported cost savings of approximately €283 (approx. £250) per patient and a reduction of 0.02 cases of colorectal cancer per patient over 10 years. Compared with this analysis the model appears more conservative with a lower estimated reduction in colorectal cancers (0.003) and lower estimated cost savings (£11.59). Clinical data in the Conway paper are based on an older version of the device (ENDOCUFF rather than ENDOCUFF VISION®), and therefore is outdated and less representative than data used in this analysis. The difference in results appears to be driven by a higher cost of colorectal cancer being used in the Conway analysis as well as exclusion of carcinoma detected during index

colonoscopy, exclusion of long term cancer progression in non-detected patients, the use of ENDOCUFF rather than ENDOCUFF VISION® data and an alternative model structure being used.

Whilst there are differences in the magnitude of results, both analyses found ENDOCUFF VISION® to be cost-saving to the health care system. In the current analysis extensive sensitivity analyses found this result to be robust when estimating the impact of parameter uncertainty on model outcomes.

9.8.2 Is the cost analysis relevant to all groups of patients and NHS settings in England that could potentially use the technology as identified in the scope?

The cost analysis is relevant to:

- People referred for colonoscopy through the NHS bowel cancer screening programme
- People offered colonoscopic surveillance because they have had adenomas removed

Both of these groups are in line with the scope. The cost analysis does not consider people offered colonoscopy after reporting symptoms to a general practitioner (which is included in the scope), because evidence around the use of ENDOCUFF VISION® in a symptomatic population has not yet demonstrated a statistically significant benefit.

Further, the results of the cost analysis may not be generalisable to areas in the NHS or patient groups with an already high baseline ADR as it is likely that the scope to benefit with ENDOCUFF VISION® would be reduced (Bhattacharyya et al. 2016b). The cost analysis is based on a baseline ADR with standard colonoscopy of 50.87%.

9.8.3 What are the main strengths and weaknesses of the analysis? How might these affect the interpretation of the results?

A key strength of the analysis is that the efficacy of the device is based on a large multicentre randomised controlled trial based in a UK NHS setting, and therefore the results of this trial should generalise well to the UK NHS. Additionally, the model structure is based upon previous published models developed to assess the cost-effectiveness of the National Bowel Cancer Screening Programme (Tappenden et al. 2007, Whyte et al. 2012a). The most recent iteration of this model was published in 2017 (Murphy et al. 2017) and was developed based upon the previously validated model published by Whyte et al (Whyte et al. 2012a). Extensive sensitivity analysis was conducted where input parameters are uncertain and the model includes the functionality to test a number of different scenarios by varying structural assumptions such as the learning curve effect, surveillance strategy and timing of colorectal cancer costs. The key weakness of the model is that the model represents a simplification of the true patient pathway in the following ways:

- Surveillance strategy for patients identified to have adenoma is a simplification of current NICE guidelines. Sensitivity analyses conducted around the surveillance strategy suggest that the implications of this are small. The impact would be greater should the strategy differ between treatment arms or should surveillance in reality be far more frequent than that recommended by NICE.

- People with incomplete colonoscopies are assumed within the model to have a follow up colonoscopy within the same cycle using ENDOCUFF VISION® if the initial colonoscopy used ENDOCUFF VISION® and otherwise with a standard colonoscopy. In these people, both the cost of the initial failed colonoscopy and the complete colonoscopy are included. Any lesions may be detected in either the first incomplete or the second complete colonoscopy. Clinical advice has indicated that some people with an incomplete colonoscopy will instead have a follow up CT scan or other diagnostic test. This has not been incorporated within the model for simplicity. However, if the sensitivity of these other tests is vastly

different or the cost of the test vastly different to colonoscopy there may be bias in the model's results. Data suggest that the difference between the proportion of complete colonoscopies in the arms of the model is small (0.1%), hence this bias will be negligible (Ngu et al. 2018b).

- The costs of CRC are applied as a one-off life time cost (in the base case), in line with the reported sources of costs of CRC by stage. This approach follows that taken in NICE guidance (National Institute for Health and Care Excellence 2011b) and in the English bowel cancer screening programme appraisal (Tappenden et al. 2007). A recent English study utilising patient level data from 275,985 patients with CRC shows that around half (£17,241) of the total healthcare costs (£38,098) are incurred in year 1 of the disease with the remainder tailing off over time (£5,014 in year 2 reducing to £1,370 in year 9), as described in Section 3.4.5 (Laudicella et al. 2016). However, the total costs in this study are higher than those used in the model, given that they include all healthcare costs, not just those specifically relating to CRC. Therefore, a proportion of the cost in each year will be for non CRC-related illness (Laudicella et al. 2016). It is possible that this proportion is greater in later years given that patients will be older and thus more likely to consume healthcare resources for other reasons. If this is the case, a greater proportion of the total CRC cost will occur in year 1, in line with the assumption made in the model. If this is not the case, and costs are incurred later than suggested within the model, the results for ENDOCUFF VISION® will be less favourable than the current results suggest, as explored in scenario analysis.

- The cost of CRC is applied such that those people with undetected carcinoma have the cost of treatment applied in the same year as their index colonoscopy. This means that the model assumes the cancer will be detected via other testing, perhaps following symptoms, within the year. Should this not be the case and people are actually detected further down the line in later model cycles, the break-even point at which ENDOCUFF VISION® becomes cost saving will be later.

9.8.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

The results of the cost analysis are likely to provide a good reflection of the impact of using ENDOCUFF VISION® in patients undergoing colonoscopy for screening or surveillance purposes in the UK NHS where the baseline ADR is around 50%. Further evidence generated in settings where the baseline ADR is lower may be of interest to determine the potential benefit of ENDOCUFF VISION® in such a setting.

Additional evidence in a symptomatic population may help to fully address the scope by identifying whether there is any benefit of using ENDOCUFF VISION® in this population group.

The analysis reports both costs and the number of CRC related deaths averted with ENDOCUFF VISION®. However, any additional mortality reduction or life years gained resulting from earlier detection of CRC (i.e. at an earlier Dukes stage) through a shift from symptom detected to screen detected cancer is not captured within the model. Thus, the analysis could be expanded to capture mortality by CRC stage and thus a difference in life years between standard colonoscopy and colonoscopy assisted with ENDOCUFF VISION®.

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Wiegering A, Ackermann S, Riegel J, et al. (2016) Improved survival of patients with colon cancer detected by screening colonoscopy. *Int J Colorectal Dis* 31,pp. 1039-1045.

Appendices

10 Appendix 1: Search Strategy for Clinical Evidence (Section 7.1.1)

The following information should be provided:

10.1.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library

We searched the following resources:

- MEDLINE, MEDLINE In-Process, MEDLINE Daily and Epub Ahead of Print (Ovid SP)
- Embase (Ovid SP)
- EconLit (Ovid SP)
- Cochrane Database of Systematic Reviews (CDSR)(Cochrane Library / Wiley)
- Cochrane Central Register of Controlled Trials (CENTRAL)(Cochrane Library / Wiley)
- Database of Abstracts of Reviews of Effects (DARE)(Cochrane Library / Wiley)
- Health Technology Assessment Database (HTA Database)(Cochrane Library / Wiley)

- NHS Economic Evaluation Database (NHS EED) (Cochrane Library / Wiley)
- Conference Proceedings Citation Index – Science (CPCI) (Web of Knowledge / Thomson Reuters)
- WHO International Clinical Trials Registry Portal (ICTRP) (http://apps.who.int/trialsearch/)
- ClinicalTrials.gov (https://clinicaltrials.gov./)
- UK Clinical Trials Gateway (https://www.ukctg.nihr.ac.uk/)
- Cost Effectiveness Analysis Registry (CEA Registry) (https://research.tufts-nemc.org/cear4/)
- U.S. Food and Drug Administration (FDA) webpage (http://www.fda.gov/)
- Conference webpages:
    - British Society of Gastroenterology Annual Meeting 2015 and 2016
    - American College of Gastroenterology Annual Scientific Meeting 2016
    - United European Gastroenterology Week 2016

10.1.2 The date on which the search was conducted.

The original searches were undertaken December 2016, and update searches were carried out in January 2017 and February 2018.

10.1.3 The date span of the search.

The database searches were limited to records with a publication date of 2010 to current.

10.1.4 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).

Details of the Original Searches

Database / information source	Number of records identified
MEDLINE, MEDLINE In-Process, MEDLINE Daily and Epub Ahead of Print (Ovid SP)	926
Embase (Ovid SP)	2,293
EconLit (Ovid SP)	0
Cochrane Database of Systematic Reviews (CDSR) (Cochrane Library / Wiley)	7
Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library / Wiley)	264
Database of Abstracts of Reviews of Effects (DARE) (Cochrane Library / Wiley)	8
Health Technology Assessment Database (HTA Database) (Cochrane Library / Wiley)	1
NHS Economic Evaluation Database (NHS EED) (Cochrane Library / Wiley)	3
Conference Proceedings Citation Index – Science (CPCI) (Web of Knowledge / Thomson Reuters)	263
WHO International Clinical Trials Registry Portal (ICTRP) http://apps.who.int/trialsearch/	17
ClinicalTrials.gov https://clinicaltrials.gov./	13
UK Clinical Trials Gateway https://www.ukctg.nihr.ac.uk/	4
Cost Effectiveness Analysis Registry (CEA Registry) https://research.tufts-nemc.org/cear4/	0
U.S. Food and Drug Administration (FDA) webpage http://www.fda.gov/	7
Conference webpages: • British Society of Gastroenterology Annual Meeting 2015 and 2016 • American College of Gastroenterology Annual Scientific Meeting 2016 • United European Gastroenterology Week 2016	10
Records supplied by client	1
Total number of records identified	**3,817**

Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>

URL/Interface: OvidSP

Database coverage dates: 1946 to present/December 1 2016

Search date 2 December 2016

Records retrieved: 926

Search strategy:

1 (endocuff$ or endo-cuff$ or ecvision$ or ec-vision$).ti,ab,kf. (15)

2 ec-assisted.ti,ab,kf. (4)

3 (aec110 or aec120 or aec130 or aec140).ti,ab,kf. (0)

4 (aec-110 or aec-120 or aec-130 or aec-140).ti,ab,kf. (0)

5 (arc medical$ or arcmedical$ or arc design$ or arcdesign$ or norgine$).ti,ab,kf,in. (36)

6 or/1-5 (53)

7 Endoscopes, Gastrointestinal/ (1632)

8 exp Colonoscopes/ (1247)

9 Endoscopy, Gastrointestinal/ (16610)

10 exp Colonoscopy/ (26400)

11 exp Colorectal Neoplasms/ (183277)

12 Colonic Polyps/ (7602)

13 (colonoscop$ or endoscop$ or sigmoidoscop$).ti,ab,kf. (195835)

14 ((bowel$1 or intestin$ or colorectal$ or colon$ or rectum$ or rectal$ or anal$ or anus or sigmoid$) adj3 (screen$ or investigat$ or diagnos$ or detect$)).ti,ab,kf. (145675)

15 ((bowel$1 or intestin$ or colorectal$ or colon$ or rectum$ or rectal$ or anal$ or anus or sigmoid$) adj3 (cancer$ or neoplasm$ or tumor$ or tumour$ or malignan$ or carcin$ or polyp$ or oncolog$ or sarcoma$ or adenocarcin$)).ti,ab,kf. (293815)

16 or/7-15 (627944)

17 ((plastic$ or flexib$ or retract$ or stretch$ or soft or novel) adj5 (tip or tips or cuff or cuffs or cap or caps or attachment$ or accessor$ or device$1 or hinge$1)).ti,ab,kf. (15332)

18 ((plastic$ or flexib$ or retract$ or stretch$ or invert$ or evert$ or soft or hinge$1) adj5 (finger$1 or branch$ or arm or arms or projection$1 or flange$1)).ti,ab,kf. (3266)

19 ((assisted or assistive) adj5 (tip or tips or cuff or cuffs or cap or caps or attachment$ or accessor$ or device$1)).ti,ab,kf. (3895)

20 or/17-19 (22287)

21 16 and 20 (1051)

22 ((colonoscop$ or endoscop$ or sigmoidoscop$) and (tip or tips or cuff or cuffs or cap or caps or attachment$ or accessor$)).ti. (388)

23 ((colonoscop$ or endoscop$ or sigmoidoscop$) adj5 (tip or tips or cuff or cuffs or cap or caps or attachment$ or accessor$)).ab,kf. (1004)

24 6 or 21 or 22 or 23 (2161)

25 exp animals/ not humans/ (4669483)

26 24 not 25 (1969)

27 limit 26 to yr="2010 -Current" (985)

28 remove duplicates from 27 (926)

Embase <1974 to 2016 December 01>

URL/Interface: OvidSP

Database coverage dates: 1974 to December 1 2016

Search date: 2 December 2016

Records retrieved: 2,293

Search strategy:

1 (endocuff$ or endo-cuff$ or ecvision$ or ec-vision$).ti,ab,kw,dv. (59)

2 ec-assisted.ti,ab,kw,dv. (11)

3 (aec110 or aec120 or aec130 or aec140).ti,ab,kw,dv. (4)

4 (aec-110 or aec-120 or aec-130 or aec-140).ti,ab,kw,dv. (0)

5 (arc medical$ or arcmedical$ or arc design$ or arcdesign$ or norgine$).ti,ab,kw,in,dm. (188)

6 or/1-5 (236)

7 digestive endoscope/ (747)

8 exp sigmoidoscope/ (324)

9 exp colonoscope/ (2831)

10 gastrointestinal endoscopy/ (28501)

11 colonoscopy/ (61090)

12 sigmoidoscopy/ (10816)

13 exp rectum tumor/ (202928)

14 exp colon tumor/ (263844)

15 exp colon polyp/ (18728)

16 (colonoscop$ or endoscop$ or sigmoidoscop$).ti,ab,kw. (285531)

17 ((bowel$1 or intestin$ or colorectal$ or colon$ or rectum$ or rectal$ or anal$ or anus or sigmoid$) adj3 (screen$ or investigat$ or diagnos$ or detect$)).ti,ab,kw. (184163)

18 ((bowel$1 or intestin$ or colorectal$ or colon$ or rectum$ or rectal$ or anal$ or anus or sigmoid$) adj3 (cancer$ or neoplasm$ or tumor$ or

tumour$ or malignan$ or carcin$ or polyp$ or oncolog$ or sarcoma$ or adenocarcin$)).ti,ab,kw. (371998)

19 or/7-18 (850560)

20 ((plastic$ or flexib$ or retract$ or stretch$ or soft or novel) adj5 (tip or tips or cuff or cuffs or cap or caps or attachment$ or accessor$ or device$1 or hinge$1)).ti,ab,kw. (16802)

21 ((plastic$ or flexib$ or retract$ or stretch$ or invert$ or evert$ or soft or hinge$1) adj5 (finger$1 or branch$ or arm or arms or projection$1 or flange$1)).ti,ab,kw. (3429)

22 ((assisted or assistive) adj5 (tip or tips or cuff or cuffs or cap or caps or attachment$ or accessor$ or device$1)).ti,ab,kw. (5113)

23 or/20-22 (25058)

24 19 and 23 (1923)

25 ((colonoscop$ or endoscop$ or sigmoidoscop$) and (tip or tips or cuff or cuffs or cap or caps or attachment$ or accessor$)).ti. (591)

26 ((colonoscop$ or endoscop$ or sigmoidoscop$) adj5 (tip or tips or cuff or cuffs or cap or caps or attachment$ or accessor$)).ab,kw. (1771)

27 6 or 24 or 25 or 26 (3843)

28 (animal/ or animal experiment/ or animal model/ or animal tissue/ or nonhuman/) not exp human/ (5358593)

29 27 not 28 (3603)

30 limit 29 to yr="2010 -Current" (2404)

31 remove duplicates from 30 (2293)

Econlit <1886 to October 2016>

URL/Interface: OvidSP

Database coverage dates: 1886 to October 2016

Search date: 2 December 2016

Records retrieved: no records retrieved

Search strategy:

1 (endocuff$ or endo-cuff$ or ecvision$ or ec-vision$).ti,ab,kw. (1)

2 ec-assisted.ti,ab,kw. (0)

3 (aec110 or aec120 or aec130 or aec140).ti,ab,kw. (0)

4 (aec-110 or aec-120 or aec-130 or aec-140).ti,ab,kw. (0)

5 (arc medical$ or arcmedical$ or arc design$ or arcdesign$ or norgine$).ti,ab,kw,in. (1)

6 or/1-5 (2)

7 (colonoscop$ or endoscop$ or sigmoidoscop$).ti,ab,kw. (40)

8 ((bowel$1 or intestin$ or colorectal$ or colon$ or rectum$ or rectal$ or anal$ or anus or sigmoid$) adj3 (screen$ or investigat$ or diagnos$ or detect$)).ti,ab,kw. (1709)

9 ((bowel$1 or intestin$ or colorectal$ or colon$ or rectum$ or rectal$ or anal$ or anus or sigmoid$) adj3 (cancer$ or neoplasm$ or tumor$ or tumour$ or malignan$ or carcin$ or polyp$ or oncolog$ or sarcoma$ or adenocarcin$)).ti,ab,kw. (158)

10 or/7-9 (1843)

11 ((plastic$ or flexib$ or retract$ or stretch$ or soft or novel) adj5 (tip or tips or cuff or cuffs or cap or caps or attachment$ or accessor$ or device$1 or hinge$1)).ti,ab,kw. (53)

12 ((plastic$ or flexib$ or retract$ or stretch$ or invert$ or evert$ or soft or hinge$1) adj5 (finger$1 or branch$ or arm or arms or projection$1 or flange$1)).ti,ab,kw. (21)

13 ((assisted or assistive) adj5 (tip or tips or cuff or cuffs or cap or caps or attachment$ or accessor$ or device$1)).ti,ab,kw. (12)

14 or/11-13 (85)

15 10 and 14 (0)

16 ((colonoscop$ or endoscop$ or sigmoidoscop$) and (tip or tips or cuff or cuffs or cap or caps or attachment$ or accessor$)).ti. (0)

17 ((colonoscop$ or endoscop$ or sigmoidoscop$) adj5 (tip or tips or cuff or cuffs or cap or caps or attachment$ or accessor$)).ab,kw. (0)

18 6 or 15 or 16 or 17 (2)

19 limit 18 to yr="2010-current" (0)

NHS Economic Evaluation Database (NHSEED)

URL/Interface: Cochrane Library, Wiley

Database coverage dates: Issue 2 of 4, April 2015

Search date: 2 December 2016

Records retrieved: 3

Search strategy:

ID	Search	Hits
#1	(endocuff* or endo-cuff* or ecvision* or ec-vision*)	11
#2	ec-assisted	2
#3	(aec110 or aec120 or aec130 or aec140)	0

#4 (aec-110 or aec-120 or aec-130 or aec-140) 0

#5 (arc next medical* or arcmedical* or arc next design* or arcdesign* or norgine*) 41

#6 #1 or #2 or #3 or #4 or #5 51

#7 MeSH descriptor: [Endoscopes, Gastrointestinal] this term only 62

#8 MeSH descriptor: [Colonoscopes] explode all trees 132

#9 MeSH descriptor: [Endoscopy, Gastrointestinal] this term only 859

#10 MeSH descriptor: [Colonoscopy] explode all trees 1843

#11 MeSH descriptor: [Colorectal Neoplasms] explode all trees 6191

#12 MeSH descriptor: [Colonic Polyps] this term only 347

#13 (colonoscop* or endoscop* or sigmoidoscop*) 21294

#14 ((bowel* or intestin* or colorectal* or colon* or rectum* or rectal* or anal* or anus or sigmoid*) near/3 (screen* or investigat* or diagnos* or detect*)) 19342

#15 ((bowel* or intestin* or colorectal* or colon* or rectum* or rectal* or anal* or anus or sigmoid*) near/3 (cancer* or neoplasm* or tumor* or tumour* or malignan* or carcin* or polyp* or oncolog* or sarcoma* or adenocarcin*)) 21723

#16 #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 54728

#17 ((plastic* or flexib* or retract* or stretch* or soft or novel) near/5 (tip or tips or cuff or cuffs or cap or caps or attachment* or accessor* or device* or hinge*)) 923

#18 ((plastic* or flexib* or retract* or stretch* or invert* or evert* or soft or hinge*) near/5 (finger* or branch* or arm or arms or projection* or flange*)) 243

#19 ((assisted or assistive) near/5 (tip or tips or cuff or cuffs or cap or caps or attachment* or accessor* or device*)) 557

#20 #17 or #18 or #19 1676

#21 #16 and #20 365

#22 ((colonoscop* or endoscop* or sigmoidoscop*) and (tip or tips or cuff or cuffs or cap or caps or attachment* or accessor*)) 545

#23 ((colonoscop* or endoscop* or sigmoidoscop*) near/5 (tip or tips or cuff or cuffs or cap or caps or attachment* or accessor*)) 178

#24 #6 or #21 or #22 or #23 Publication Year from 2010 to 2016, in Economic Evaluations 3

Health Technology Assessment (HTA)

URL/Interface: Cochrane Library, Wiley

Database coverage dates: Issue 4 of 4, October 2016

Search date: 2 December 2016

Records retrieved: 1

Search strategy: see below

ID Search Hits

#1 (endocuff* or endo-cuff* or ecvision* or ec-vision*) 11

#2 ec-assisted 2

#3 (aec110 or aec120 or aec130 or aec140) 0

#4 (aec-110 or aec-120 or aec-130 or aec-140) 0

#5 (arc next medical* or arcmedical* or arc next design* or arcdesign* or norgine*) 41

#6 #1 or #2 or #3 or #4 or #5 51

#7 MeSH descriptor: [Endoscopes, Gastrointestinal] this term only 62

#8 MeSH descriptor: [Colonoscopes] explode all trees 132

#9 MeSH descriptor: [Endoscopy, Gastrointestinal] this term only 859

#10 MeSH descriptor: [Colonoscopy] explode all trees 1843

#11 MeSH descriptor: [Colorectal Neoplasms] explode all trees 6191

#12 MeSH descriptor: [Colonic Polyps] this term only 347

#13 (colonoscop* or endoscop* or sigmoidoscop*) 21294

#14 ((bowel* or intestin* or colorectal* or colon* or rectum* or rectal* or anal* or anus or sigmoid*) near/3 (screen* or investigat* or diagnos* or detect*)) 19342

#15 ((bowel* or intestin* or colorectal* or colon* or rectum* or rectal* or anal* or anus or sigmoid*) near/3 (cancer* or neoplasm* or tumor* or tumour* or malignan* or carcin* or polyp* or oncolog* or sarcoma* or adenocarcin*)) 21723

#16 #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 54728

#17 ((plastic* or flexib* or retract* or stretch* or soft or novel) near/5 (tip or tips or cuff or cuffs or cap or caps or attachment* or accessor* or device* or hinge*)) 923

#18 ((plastic* or flexib* or retract* or stretch* or invert* or evert* or soft or hinge*) near/5 (finger* or branch* or arm or arms or projection* or flange*)) 243

#19 ((assisted or assistive) near/5 (tip or tips or cuff or cuffs or cap or caps or attachment* or accessor* or device*)) 557

#20 #17 or #18 or #19 1676

#21 #16 and #20 365

#22 ((colonoscop* or endoscop* or sigmoidoscop*) and (tip or tips or cuff or cuffs or cap or caps or attachment* or accessor*)) 545

#23 ((colonoscop* or endoscop* or sigmoidoscop*) near/5 (tip or tips or cuff or cuffs or cap or caps or attachment* or accessor*)) 178

#24 #6 or #21 or #22 or #23 Publication Year from 2010 to 2016, in Technology Assessments 1

Cochrane Central Register of Controlled Trials (CENTRAL)

URL/Interface: Cochrane Library, Wiley

Database coverage dates: Issue 11 of 12, November 2016

Search date: 2 December 2016

Records retrieved: 264

Search strategy: see below

ID Search Hits

#1 (endocuff* or endo-cuff* or ecvision* or ec-vision*) 11

#2 ec-assisted 2

#3 (aec110 or aec120 or aec130 or aec140) 0

#4 (aec-110 or aec-120 or aec-130 or aec-140) 0

#5 (arc next medical* or arcmedical* or arc next design* or arcdesign* or norgine*) 41

#6 #1 or #2 or #3 or #4 or #5 51

#7 MeSH descriptor: [Endoscopes, Gastrointestinal] this term only 62

#8 MeSH descriptor: [Colonoscopes] explode all trees 132

#9	MeSH descriptor: [Endoscopy, Gastrointestinal] this term only	859
#10	MeSH descriptor: [Colonoscopy] explode all trees	1843
#11	MeSH descriptor: [Colorectal Neoplasms] explode all trees	6191
#12	MeSH descriptor: [Colonic Polyps] this term only	347
#13	(colonoscop* or endoscop* or sigmoidoscop*)	21294
#14	((bowel* or intestin* or colorectal* or colon* or rectum* or rectal* or anal* or anus or sigmoid*) near/3 (screen* or investigat* or diagnos* or detect*))	19342
#15	((bowel* or intestin* or colorectal* or colon* or rectum* or rectal* or anal* or anus or sigmoid*) near/3 (cancer* or neoplasm* or tumor* or tumour* or malignan* or carcin* or polyp* or oncolog* or sarcoma* or adenocarcin*))	21723
#16	#7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15	54728
#17	((plastic* or flexib* or retract* or stretch* or soft or novel) near/5 (tip or tips or cuff or cuffs or cap or caps or attachment* or accessor* or device* or hinge*))	923
#18	((plastic* or flexib* or retract* or stretch* or invert* or evert* or soft or hinge*) near/5 (finger* or branch* or arm or arms or projection* or flange*))	243
#19	((assisted or assistive) near/5 (tip or tips or cuff or cuffs or cap or caps or attachment* or accessor* or device*))	557
#20	#17 or #18 or #19	1676
#21	#16 and #20	365
#22	((colonoscop* or endoscop* or sigmoidoscop*) and (tip or tips or cuff or cuffs or cap or caps or attachment* or accessor*))	545

#23 ((colonoscop* or endoscop* or sigmoidoscop*) near/5 (tip or tips or cuff or cuffs or cap or caps or attachment* or accessor*)) 178

#24 #6 or #21 or #22 or #23 Publication Year from 2010 to 2016, in Trials 264

Database of Abstracts of Reviews of Effectiveness (DARE)

URL/Interface: Cochrane Library, Wiley

Database coverage dates: Issue 2 of 4, April 2015

Search date: 2 December 2016

Records retrieved: 8

Search strategy: see below

ID	Search	Hits
#1	(endocuff* or endo-cuff* or ecvision* or ec-vision*)	11
#2	ec-assisted	2
#3	(aec110 or aec120 or aec130 or aec140)	0
#4	(aec-110 or aec-120 or aec-130 or aec-140)	0
#5	(arc next medical* or arcmedical* or arc next design* or arcdesign* or norgine*)	41
#6	#1 or #2 or #3 or #4 or #5	51
#7	MeSH descriptor: [Endoscopes, Gastrointestinal] this term only	62
#8	MeSH descriptor: [Colonoscopes] explode all trees	132
#9	MeSH descriptor: [Endoscopy, Gastrointestinal] this term only	859
#10	MeSH descriptor: [Colonoscopy] explode all trees	1843
#11	MeSH descriptor: [Colorectal Neoplasms] explode all trees	6191

#12 MeSH descriptor: [Colonic Polyps] this term only 347

#13 (colonoscop* or endoscop* or sigmoidoscop*) 21294

#14 ((bowel* or intestin* or colorectal* or colon* or rectum* or rectal* or anal* or anus or sigmoid*) near/3 (screen* or investigat* or diagnos* or detect*)) 19342

#15 ((bowel* or intestin* or colorectal* or colon* or rectum* or rectal* or anal* or anus or sigmoid*) near/3 (cancer* or neoplasm* or tumor* or tumour* or malignan* or carcin* or polyp* or oncolog* or sarcoma* or adenocarcin*)) 21723

#16 #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 54728

#17 ((plastic* or flexib* or retract* or stretch* or soft or novel) near/5 (tip or tips or cuff or cuffs or cap or caps or attachment* or accessor* or device* or hinge*)) 923

#18 ((plastic* or flexib* or retract* or stretch* or invert* or evert* or soft or hinge*) near/5 (finger* or branch* or arm or arms or projection* or flange*)) 243

#19 ((assisted or assistive) near/5 (tip or tips or cuff or cuffs or cap or caps or attachment* or accessor* or device*)) 557

#20 #17 or #18 or #19 1676

#21 #16 and #20 365

#22 ((colonoscop* or endoscop* or sigmoidoscop*) and (tip or tips or cuff or cuffs or cap or caps or attachment* or accessor*)) 545

#23 ((colonoscop* or endoscop* or sigmoidoscop*) near/5 (tip or tips or cuff or cuffs or cap or caps or attachment* or accessor*)) 178

#24 #6 or #21 or #22 or #23 Publication Year from 2010 to 2016, in Other Reviews 8

Cochrane Database of Systematic Reviews (CDSR)

URL/Interface: Cochrane Library, Wiley

Database coverage dates: Issue 12 of 12, December 2016

Search date: 2 December 2016

Records retrieved: 7

Search strategy: see below

ID	Search	Hits
#1	(endocuff* or endo-cuff* or ecvision* or ec-vision*):ti,ab,kw	11
#2	ec-assisted:ti,ab,kw	2
#3	(aec110 or aec120 or aec130 or aec140):ti,ab,kw	0
#4	(aec-110 or aec-120 or aec-130 or aec-140):ti,ab,kw	0
#5	(arc next medical* or arcmedical* or arc next design* or arcdesign* or norgine*):ti,ab,kw	6
#6	#1 or #2 or #3 or #4 or #5	16
#7	MeSH descriptor: [Endoscopes, Gastrointestinal] this term only	62
#8	MeSH descriptor: [Colonoscopes] explode all trees	132
#9	MeSH descriptor: [Endoscopy, Gastrointestinal] this term only	859
#10	MeSH descriptor: [Colonoscopy] explode all trees	1843
#11	MeSH descriptor: [Colorectal Neoplasms] explode all trees	6191
#12	MeSH descriptor: [Colonic Polyps] this term only	347
#13	(colonoscop* or endoscop* or sigmoidoscop*):ti,ab,kw	18142

#14 ((bowel* or intestin* or colorectal* or colon* or rectum* or rectal* or anal* or anus or sigmoid*) near/3 (screen* or investigat* or diagnos* or detect*)):ti,ab,kw 11038

#15 ((bowel* or intestin* or colorectal* or colon* or rectum* or rectal* or anal* or anus or sigmoid*) near/3 (cancer* or neoplasm* or tumor* or tumour* or malignan* or carcin* or polyp* or oncolog* or sarcoma* or adenocarcin*)):ti,ab,kw 20314

#16 #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 43951

#17 ((plastic* or flexib* or retract* or stretch* or soft or novel) near/5 (tip or tips or cuff or cuffs or cap or caps or attachment* or accessor* or device* or hinge*)):ti,ab,kw 810

#18 ((plastic* or flexib* or retract* or stretch* or invert* or evert* or soft or hinge*) near/5 (finger* or branch* or arm or arms or projection* or flange*)):ti,ab,kw 163

#19 ((assisted or assistive) near/5 (tip or tips or cuff or cuffs or cap or caps or attachment* or accessor* or device*)):ti,ab,kw 395

#20 #17 or #18 or #19 1348

#21 #16 and #20 129

#22 ((colonoscop* or endoscop* or sigmoidoscop*) and (tip or tips or cuff or cuffs or cap or caps or attachment* or accessor*)):ti 88

#23 ((colonoscop* or endoscop* or sigmoidoscop*) near/5 (tip or tips or cuff or cuffs or cap or caps or attachment* or accessor*)):ab,kw 118

#24 #6 or #21 or #22 or #23 Online Publication Date from Jan 2010 to Nov 2016, in Cochrane Reviews (Reviews and Protocols) 7

Conference Proceedings Citation Index – Science (CPCI-S)

URL/Interface: Web of Knowledge/Thomson Reuters

Database coverage dates: 1990-current

Search date:

Records retrieved:

Search strategy: see below

18

263

#6 OR #15 OR #16 OR #17

Indexes=CPCI-S Timespan=2010-2016

17

68

TS=((colonoscop* OR endoscop* OR sigmoidoscop*) NEAR/5 ("tip" OR "tips" OR "cuff" OR "cuffs" OR "cap" OR "caps" OR attachment* OR accessor*))

Indexes=CPCI-S Timespan=2010-2016

16

36

TI=((colonoscop* OR endoscop* OR sigmoidoscop*) AND ("tip" OR "tips" OR "cuff" OR "cuffs" OR "cap" OR "caps" OR attachment* OR accessor*))

15

138

#10 AND #14

Indexes=CPCI-S Timespan=2010-2016

14

6,430

#11 OR #12 OR #13

Indexes=CPCI-S Timespan=2010-2016

13

735

TS=(("assisted" OR "assistive") NEAR/5 ("tip" OR "tips" OR "cuff" OR "cuffs" OR "cap" OR "caps" OR attachment* OR accessor* OR device$))

Indexes=CPCI-S Timespan=2010-2016

12

627

TS=((plastic* OR flexib* OR retract* OR stretch* OR invert* OR evert* OR "soft" OR hinge$) NEAR/5 (finger$ OR branch* OR "arm" OR "arms" OR projection$ OR flange$))

Indexes=CPCI-S Timespan=2010-2016

11

5,144

TS=((plastic* OR flexib* OR retract* OR stretch* OR "soft" OR "novel") NEAR/5 ("tip" OR "tips" OR "cuff" OR "cuffs" OR "cap" OR "caps" OR attachment* OR accessor* OR device$ OR hinge$))

Indexes=CPCI-S Timespan=2010-2016

10

44,713

#7 OR #8 OR #9

Indexes=CPCI-S Timespan=2010-2016

9

18,687

TS=((bowel$ OR intestin* OR colorectal* OR colon* OR rectum* OR rectal* OR anal* OR "anus" OR sigmoid*) NEAR/3 (cancer* OR neoplasm* OR tumor* OR tumour* OR malignan* OR carcin* OR polyp* OR oncolog* OR sarcoma* OR adenocarcin*))

Indexes=CPCI-S Timespan=2010-2016

8

19,630

TS=((bowel$ OR intestin* OR colorectal* OR colon* OR rectum* OR rectal* OR anal* OR "anus" OR sigmoid*) NEAR/3 (screen* OR investigat* OR diagnos* OR detect*))

Indexes=CPCI-S Timespan=2010-2016

7

9,160

TS=(colonoscop* OR endoscop* OR sigmoidoscop*)

Indexes=CPCI-S Timespan=2010-2016

6

74

#1 OR #2 OR #3 OR #4 OR #5

Indexes=CPCI-S Timespan=2010-2016

5

65

OG=(arc NEAR/0 medical* OR arcmedical* OR arc NEAR/0 design* OR arcdesign* OR norgine*) OR AD=(arc NEAR/0 medical* OR arcmedical* OR arc NEAR/0 design* OR arcdesign* OR norgine*) OR SG=(arc NEAR/0 medical* OR arcmedical* OR arc NEAR/0 design* OR arcdesign* or norgine*) OR FO=(arc NEAR/0 medical* OR arcmedical* OR arc NEAR/0 design* OR arcdesign* OR norgine*) OR TS=(arc NEAR/0 medical* OR arcmedical* OR arc NEAR/0 design* OR arcdesign* OR norgine*)

Indexes=CPCI-S Timespan=2010-2016

4

0

TS=("aec-110" OR "aec-120" OR "aec-130" OR "aec-140")

Indexes=CPCI-S Timespan=2010-2016

3

0

TS=("aec110" OR "aec120" OR "aec130" OR "aec140")

Indexes=CPCI-S Timespan=2010-2016

2

2

TS="ec-assisted"

Indexes=CPCI-S Timespan=2010-2016

1

7

TS=(endocuff* or endo-cuff* or ecvision* or ec-vision*)

Indexes=CPCI-S Timespan=2010-2016

WHO International Clinical Trials Registry Portal (ICTRP)

URL/Interface: http://apps.who.int/trialsearch/

Database coverage dates: not indicated

Search date: 2 December 2016

Records retrieved: 17

Search strategy: see below

The default search screen was used.

endocuff OR endo-cuff OR ecvision OR ec-vision OR ec-assisted OR aec110 OR aec120 OR aec130 OR aec140 OR aec-110 OR aec-120 OR aec-130 OR aec-140

ClinicalTrials.gov

URL/Interface: https://clinicaltrials.gov./

Database coverage dates: not indicated

Search date: 2 December 2016

Records retrieved: 13

Search strategy: see below

The “Advanced Search” screen was used. Terms were searched using the “Search Terms” field.

endocuff OR endo-cuff OR ecvision OR ec-vision OR ec-assisted OR aec110 OR aec120 OR aec130 OR aec140 OR aec-110 OR aec-120 OR aec-130 OR aec-140

UK Clinical Trials Gateway

URL/Interface: https://www.ukctg.nihr.ac.uk/

Database coverage dates: not indicated

Search date: 2 December 2016

Records retrieved: 4

Only a basic search option is available. Truncation seems to be automatic. Use of Boolean operators is not allowed. The system seems to perform an implicit “AND” operation if two or more terms are used.

All statuses were selected from “Trial Status” option on the result page.

endocuff 4 results

endo-cuff: 1 result (the same record was found by endocuff and was not downloaded)

ecvision no results

ec-vision: no results

ec-assisted: no results

aec110: no results

aec120: no results

aec130: no results

aec140: no results

aec-110: no results

aec-120: no results

aec-130: no results

aec-140: no results

Cost Effectiveness Analysis Registry (CEA Registry)

Interface/URL: http://healtheconomics.tuftsmedicalcenter.org/cear4/Home.aspx

Database coverage dates: 1976 to current

Search date: 2 December 2016

Records retrieved: No records retrieved

Search strategy: see below

Basic search option was used.

endocuff: no results

endo-cuff: no results

ecvision no results

ec-vision: no results

aec110: no results

aec120: no results

aec130: no results

aec140: no results

aec-110: no results

aec-120: no results

aec-130: no results

aec-140: no results

U.S. Food and Drug Administration (FDA)

Interface/URL: http://www.fda.gov/

Database coverage dates: not indicated

Search date: 30 November 2016

Records retrieved: 7

Search strategy: see below

Site wide search functionality was used.

endocuff: 7 results

endo-cuff: no results

ecvision no results

ec-vision: no results

ec-assisted: no results

aec110: no results

aec120: no results

aec130: no results

aec140: no results

aec-110: no results

aec-120: no results

aec-130: no results

aec-140: no results

American College of Gastroenterology Annual Scientific Meeting 2016

Interface/URL:

http://acgmeetings.gi.org/

https://www.eventscribe.com/2016/ACG/SearchPostersByKeyword.asp# (Poster search)

https://www.eventscribe.com/2016/ACG/SearchByKeyword.asp
(Courses/Session search)

Search date: 28 November 2016

Records retrieved: 1

Search strategy: see below

Keywords were searched individually. It was not possible to use truncation. Use of Boolean operators was not possible.

Poster search:

endocuff: 1 result

endo-cuff: no results

ecvision: no results

ec-vision: no results

ec-assisted: results

aec110: no results

aec120: no results

aec130: no results

aec140: no results

aec-110: no results

aec-120: no results

aec-130: no results

aec-140: no results

Courses/Session search:

endocuff: no results

endo-cuff: no results

ecvision: no results

ec-vision: no results

ec-assisted: results

aec110: no results

aec120: no results

aec130: no results

aec140: no results

aec-110: no results

aec-120: no results

aec-130: no results

aec-140: no results

United European Gastroenterology Week 2016

Interface/URL:

https://www.ueg.eu/week/

https://www.ueg.eu/education/library/#stq=%20&stp=1?abstract2016=true

Search date: 28 November 2016

Records retrieved: 6

Search strategy: see below

Keywords were searched individually. Truncation seemed automatic. Hyphenated words and terms containing both numbers and words needed to be encased in

quotation marks to increase precision (words appearing together rather than anywhere in the document separately). It was not possible to use Boolean operators.

endocuff: 6 results

“endo-cuff”: no results

ecvision: no results

“ec-vision”: no results

“ec-assisted”: no results

“aec110”: no results

“aec120”: no results

“aec130”: no results

“aec140”: no results

“aec-110”: no results

“aec-120”: no results

“aec-130”: no results

“aec-140”: no results

British Society of Gastroenterology Annual Meeting 2015 and 2016

Interface/URL:

http://www.bsg.org.uk/education/meeting/index.html

http://www.bsg.org.uk/images/stories/docs/bsg_abstracts_16.pdf

http://www.bsg.org.uk/images/stories/docs/education/bsg_abstracts_15.pdf

Search date: 2 December 2016

Records retrieved: 3

Search strategy: see below

Abstract books for the annual meetings were searched using ctrl+f

endocuff: 3 results

endo-cuff: no results

ecvision: no results

ec-vision: no results

ec-assisted: results

aec110: no results

aec120: no results

aec130: no results

aec140: no results

aec-110: no results

aec-120: no results

aec-130: no results

aec-140: no results

Details of the Update Search – January 2017)

Database / information source	Number of records identified
MEDLINE, MEDLINE In-Process, MEDLINE Daily and Epub Ahead of Print (Ovid SP)	946
Embase (Ovid SP)	2,332
EconLit (Ovid SP)	0
Cochrane Database of Systematic Reviews (CDSR) (Cochrane Library / Wiley)	8
Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library / Wiley)	264
Health Technology Assessment Database (HTA Database) (Cochrane Library / Wiley)	8
Conference Proceedings Citation Index – Science (CPCI) (Web of Knowledge / Thomson Reuters)	275
WHO International Clinical Trials Registry Portal (ICTRP) http://apps.who.int/trialsearch/	17
ClinicalTrials.gov https://clinicaltrials.gov./	13
UK Clinical Trials Gateway https://www.ukctg.nihr.ac.uk/	4
Cost Effectiveness Analysis Registry (CEA Registry) https://research.tufts-nemc.org/cear4/	0
U.S. Food and Drug Administration (FDA) webpage http://www.fda.gov/	14
Additional records supplied by client after original searches	2
Total number of records identified	**3,883**

The searches of NHS EED and DARE were not updated as these resources closed to new records in 2015. No new records could have been added since the original search.

Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)

URL/Interface: OvidSP

Database coverage dates: 1946 to present

Search date: 11 January 2017

Records retrieved: 946

Search strategy:

1 (endocuff$ or endo-cuff$ or ecvision$ or ec-vision$).ti,ab,kf. (19)

2 ec-assisted.ti,ab,kf. (5)

3 (aec110 or aec120 or aec130 or aec140).ti,ab,kf. (0)

4 (aec-110 or aec-120 or aec-130 or aec-140).ti,ab,kf. (0)

5 (arc medical$ or arcmedical$ or arc design$ or arcdesign$ or norgine$).ti,ab,kf,in. (41)

6 or/1-5 (62)

7 Endoscopes, Gastrointestinal/ (1795)

8 exp Colonoscopes/ (1385)

9 Endoscopy, Gastrointestinal/ (17864)

10 exp Colonoscopy/ (28560)

11 exp Colorectal Neoplasms/ (192597)

12 Colonic Polyps/ (8039)

13 (colonoscop$ or endoscop$ or sigmoidoscop$).ti,ab,kf. (208386)

14 ((bowel$1 or intestin$ or colorectal$ or colon$ or rectum$ or rectal$ or anal$ or anus or sigmoid$) adj3 (screen$ or investigat$ or diagnos$ or detect$)).ti,ab,kf. (152189)

15 ((bowel$1 or intestin$ or colorectal$ or colon$ or rectum$ or rectal$ or anal$ or anus or sigmoid$) adj3 (cancer$ or neoplasm$ or tumor$ or tumour$ or malignan$ or carcin$ or polyp$ or oncolog$ or sarcoma$ or adenocarcin$)).ti,ab,kf. (309609)

16 or/7-15 (662846)

17 ((plastic$ or flexib$ or retract$ or stretch$ or soft or novel) adj5 (tip or tips or cuff or cuffs or cap or caps or attachment$ or accessor$ or device$1 or hinge$1)).ti,ab,kf. (15960)

18 ((plastic$ or flexib$ or retract$ or stretch$ or invert$ or evert$ or soft or hinge$1) adj5 (finger$1 or branch$ or arm or arms or projection$1 or flange$1)).ti,ab,kf. (3398)

19 ((assisted or assistive) adj5 (tip or tips or cuff or cuffs or cap or caps or attachment$ or accessor$ or device$1)).ti,ab,kf. (4056)

20 or/17-19 (23201)

21 16 and 20 (1113)

22 ((colonoscop$ or endoscop$ or sigmoidoscop$) and (tip or tips or cuff or cuffs or cap or caps or attachment$ or accessor$)).ti. (422)

23 ((colonoscop$ or endoscop$ or sigmoidoscop$) adj5 (tip or tips or cuff or cuffs or cap or caps or attachment$ or accessor$)).ab,kf. (1077)

24 6 or 21 or 22 or 23 (2309)

25 exp animals/ not humans/ (4853216)

26 24 not 25 (2104)

27 limit 26 to yr="2010 -Current" (1035)

28 remove duplicates from 27 (946)

Embase <1974 to 2017 January 10>

URL/Interface: OvidSP

Database coverage dates: 1974-10 January 2017

Search date: 11 January 2017

Records retrieved: 2,332

Search strategy:

1 (endocuff$ or endo-cuff$ or ecvision$ or ec-vision$).ti,ab,kw,dv. (62)

2 ec-assisted.ti,ab,kw,dv. (11)

3 (aec110 or aec120 or aec130 or aec140).ti,ab,kw,dv. (4)

4 (aec-110 or aec-120 or aec-130 or aec-140).ti,ab,kw,dv. (0)

5 (arc medical$ or arcmedical$ or arc design$ or arcdesign$ or norgine$).ti,ab,kw,in,dm. (191)

6 or/1-5 (241)

7 digestive endoscope/ (776)

8 exp sigmoidoscope/ (326)

9 exp colonoscope/ (2869)

10 gastrointestinal endoscopy/ (28778)

11 colonoscopy/ (61758)

12 sigmoidoscopy/ (10915)

13 exp rectum tumor/ (205582)

14 exp colon tumor/ (267106)

15 exp colon polyp/ (18865)

16 (colonoscop$ or endoscop$ or sigmoidoscop$).ti,ab,kw. (288034)

17 ((bowel$1 or intestin$ or colorectal$ or colon$ or rectum$ or rectal$ or anal$ or anus or sigmoid$) adj3 (screen$ or investigat$ or diagnos$ or detect$)).ti,ab,kw. (186123)

18 ((bowel$1 or intestin$ or colorectal$ or colon$ or rectum$ or rectal$ or anal$ or anus or sigmoid$) adj3 (cancer$ or neoplasm$ or tumor$ or

tumour$ or malignan$ or carcin$ or polyp$ or oncolog$ or sarcoma$ or adenocarcin$)).ti,ab,kw. (376949)

19 or/7-18 (859929)

20 ((plastic$ or flexib$ or retract$ or stretch$ or soft or novel) adj5 (tip or tips or cuff or cuffs or cap or caps or attachment$ or accessor$ or device$1 or hinge$1)).ti,ab,kw. (17001)

21 ((plastic$ or flexib$ or retract$ or stretch$ or invert$ or evert$ or soft or hinge$1) adj5 (finger$1 or branch$ or arm or arms or projection$1 or flange$1)).ti,ab,kw. (3459)

22 ((assisted or assistive) adj5 (tip or tips or cuff or cuffs or cap or caps or attachment$ or accessor$ or device$1)).ti,ab,kw. (5163)

23 or/20-22 (25330)

24 19 and 23 (1945)

25 ((colonoscop$ or endoscop$ or sigmoidoscop$) and (tip or tips or cuff or cuffs or cap or caps or attachment$ or accessor$)).ti. (598)

26 ((colonoscop$ or endoscop$ or sigmoidoscop$) adj5 (tip or tips or cuff or cuffs or cap or caps or attachment$ or accessor$)).ab,kw. (1791)

27 6 or 24 or 25 or 26 (3885)

28 (animal/ or animal experiment/ or animal model/ or animal tissue/ or nonhuman/) not exp human/ (5387048)

29 27 not 28 (3644)

30 limit 29 to yr="2010 -Current" (2445)

31 remove duplicates from 30 (2332)

Econlit <1886 to October 2016>

URL/Interface: OvidSP

Database coverage dates: 1886 to December 2016

Search date: 11 January 2017

Records retrieved: 0

Search strategy:

Database: Econlit <

Search Strategy:

1 (endocuff$ or endo-cuff$ or ecvision$ or ec-vision$).ti,ab,kw. (1)

2 ec-assisted.ti,ab,kw. (0)

3 (aec110 or aec120 or aec130 or aec140).ti,ab,kw. (0)

4 (aec-110 or aec-120 or aec-130 or aec-140).ti,ab,kw. (0)

5 (arc medical$ or arcmedical$ or arc design$ or arcdesign$ or norgine$).ti,ab,kw,in. (1)

6 or/1-5 (2)

7 (colonoscop$ or endoscop$ or sigmoidoscop$).ti,ab,kw. (41)

8 ((bowel$1 or intestin$ or colorectal$ or colon$ or rectum$ or rectal$ or anal$ or anus or sigmoid$) adj3 (screen$ or investigat$ or diagnos$ or detect$)).ti,ab,kw. (1733)

9 ((bowel$1 or intestin$ or colorectal$ or colon$ or rectum$ or rectal$ or anal$ or anus or sigmoid$) adj3 (cancer$ or neoplasm$ or tumor$ or tumour$ or malignan$ or carcin$ or polyp$ or oncolog$ or sarcoma$ or adenocarcin$)).ti,ab,kw. (159)

10 or/7-9 (1867)

11 ((plastic$ or flexib$ or retract$ or stretch$ or soft or novel) adj5 (tip or tips or cuff or cuffs or cap or caps or attachment$ or accessor$ or device$1 or hinge$1)).ti,ab,kw. (55)

12 ((plastic$ or flexib$ or retract$ or stretch$ or invert$ or evert$ or soft or hinge$1) adj5 (finger$1 or branch$ or arm or arms or projection$1 or flange$1)).ti,ab,kw. (21)

13 ((assisted or assistive) adj5 (tip or tips or cuff or cuffs or cap or caps or attachment$ or accessor$ or device$1)).ti,ab,kw. (12)

14 or/11-13 (87)

15 10 and 14 (0)

16 ((colonoscop$ or endoscop$ or sigmoidoscop$) and (tip or tips or cuff or cuffs or cap or caps or attachment$ or accessor$)).ti. (0)

17 ((colonoscop$ or endoscop$ or sigmoidoscop$) adj5 (tip or tips or cuff or cuffs or cap or caps or attachment$ or accessor$)).ab,kw. (0)

18 6 or 15 or 16 or 17 (2)

19 limit 18 to yr="2010-current" (0)

Health Technology Assessment (HTA) Database

URL/Interface: Cochrane Library, Wiley

Database coverage dates: Issue 4 of 4, October 2016

Search date: 11 January 2017

Records retrieved: 8

Search strategy:

#1 (endocuff* or endo-cuff* or ecvision* or ec-vision*) 11

#2 ec-assisted 2

#3 (aec110 or aec120 or aec130 or aec140) 0

#4 (aec-110 or aec-120 or aec-130 or aec-140) 0

#5 (arc next medical* or arcmedical* or arc next design* or arcdesign* or norgine*) 42

#6 #1 or #2 or #3 or #4 or #5 52

#7 MeSH descriptor: [Endoscopes, Gastrointestinal] this term only 62

#8 MeSH descriptor: [Colonoscopes] explode all trees 132

#9 MeSH descriptor: [Endoscopy, Gastrointestinal] this term only 859

#10 MeSH descriptor: [Colonoscopy] explode all trees 1843

#11 MeSH descriptor: [Colorectal Neoplasms] explode all trees 6191

#12 MeSH descriptor: [Colonic Polyps] this term only 347

#13 (colonoscop* or endoscop* or sigmoidoscop*) 21299

#14 ((bowel* or intestin* or colorectal* or colon* or rectum* or rectal* or anal* or anus or sigmoid*) near/3 (screen* or investigat* or diagnos* or detect*)) 19389

#15 ((bowel* or intestin* or colorectal* or colon* or rectum* or rectal* or anal* or anus or sigmoid*) near/3 (cancer* or neoplasm* or tumor* or tumour* or malignan* or carcin* or polyp* or oncolog* or sarcoma* or adenocarcin*)) 21732

#16 #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 54775

#17 ((plastic* or flexib* or retract* or stretch* or soft or novel) near/5 (tip or tips or cuff or cuffs or cap or caps or attachment* or accessor* or device* or hinge*)) 923

#18 ((plastic* or flexib* or retract* or stretch* or invert* or evert* or soft or hinge*) near/5 (finger* or branch* or arm or arms or projection* or flange*)) 244

#19 ((assisted or assistive) near/5 (tip or tips or cuff or cuffs or cap or caps or attachment* or accessor* or device*)) 557

#20 #17 or #18 or #19 1677

#21 #16 and #20 367

#22 ((colonoscop* or endoscop* or sigmoidoscop*) and (tip or tips or cuff or cuffs or cap or caps or attachment* or accessor*)) 546

#23 ((colonoscop* or endoscop* or sigmoidoscop*) near/5 (tip or tips or cuff or cuffs or cap or caps or attachment* or accessor*)) 177

#24 #6 or #21 or #22 or #23 Publication Year from 2010 to 2017, in Technology Assessments 1

Cochrane Central Register of Controlled Trials (CENTRAL)

URL/Interface: Cochrane Library, Wiley

Database coverage dates: Issue 11 of 12, November 2016

Search date: 11 January 2017

Records retrieved: 264

Search strategy:

#1 (endocuff* or endo-cuff* or ecvision* or ec-vision*) 11

#2 ec-assisted 2

#3 (aec110 or aec120 or aec130 or aec140) 0

#4 (aec-110 or aec-120 or aec-130 or aec-140) 0

#5	(arc next medical* or arcmedical* or arc next design* or arcdesign* or norgine*)	42
#6	#1 or #2 or #3 or #4 or #5	52
#7	MeSH descriptor: [Endoscopes, Gastrointestinal] this term only	62
#8	MeSH descriptor: [Colonoscopes] explode all trees	132
#9	MeSH descriptor: [Endoscopy, Gastrointestinal] this term only	859
#10	MeSH descriptor: [Colonoscopy] explode all trees	1843
#11	MeSH descriptor: [Colorectal Neoplasms] explode all trees	6191
#12	MeSH descriptor: [Colonic Polyps] this term only	347
#13	(colonoscop* or endoscop* or sigmoidoscop*)	21299
#14	((bowel* or intestin* or colorectal* or colon* or rectum* or rectal* or anal* or anus or sigmoid*) near/3 (screen* or investigat* or diagnos* or detect*))	19389
#15	((bowel* or intestin* or colorectal* or colon* or rectum* or rectal* or anal* or anus or sigmoid*) near/3 (cancer* or neoplasm* or tumor* or tumour* or malignan* or carcin* or polyp* or oncolog* or sarcoma* or adenocarcin*))	21732
#16	#7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15	54775
#17	((plastic* or flexib* or retract* or stretch* or soft or novel) near/5 (tip or tips or cuff or cuffs or cap or caps or attachment* or accessor* or device* or hinge*))	923
#18	((plastic* or flexib* or retract* or stretch* or invert* or evert* or soft or hinge*) near/5 (finger* or branch* or arm or arms or projection* or flange*))	244

#19 ((assisted or assistive) near/5 (tip or tips or cuff or cuffs or cap or caps or attachment* or accessor* or device*)) 557

#20 #17 or #18 or #19 1677

#21 #16 and #20 367

#22 ((colonoscop* or endoscop* or sigmoidoscop*) and (tip or tips or cuff or cuffs or cap or caps or attachment* or accessor*)) 546

#23 ((colonoscop* or endoscop* or sigmoidoscop*) near/5 (tip or tips or cuff or cuffs or cap or caps or attachment* or accessor*)) 177

#24 #6 or #21 or #22 or #23 Publication Year from 2010 to 2017, in Trials 264

Cochrane Database of Systematic Reviews (CDSR)

URL/Interface: Cochrane Library, Wiley

Database coverage dates: Issue 1 of 12, January 2017

Search date: 11 January 2017

Records retrieved: 8

Search strategy:

#1 (endocuff* or endo-cuff* or ecvision* or ec-vision*):ti,ab,kw 11

#2 ec-assisted:ti,ab,kw 2

#3 (aec110 or aec120 or aec130 or aec140):ti,ab,kw 0

#4 (aec-110 or aec-120 or aec-130 or aec-140):ti,ab,kw 0

#5 (arc next medical* or arcmedical* or arc next design* or arcdesign* or norgine*):ti,ab,kw 6

#6 #1 or #2 or #3 or #4 or #5 16

#7 MeSH descriptor: [Endoscopes, Gastrointestinal] this term only 62

#8 MeSH descriptor: [Colonoscopes] explode all trees 132

#9 MeSH descriptor: [Endoscopy, Gastrointestinal] this term only 859

#10 MeSH descriptor: [Colonoscopy] explode all trees 1843

#11 MeSH descriptor: [Colorectal Neoplasms] explode all trees 6191

#12 MeSH descriptor: [Colonic Polyps] this term only 347

#13 (colonoscop* or endoscop* or sigmoidoscop*):ti,ab,kw 18143

#14 ((bowel* or intestin* or colorectal* or colon* or rectum* or rectal* or anal* or anus or sigmoid*) near/3 (screen* or investigat* or diagnos* or detect*)):ti,ab,kw 11062

#15 ((bowel* or intestin* or colorectal* or colon* or rectum* or rectal* or anal* or anus or sigmoid*) near/3 (cancer* or neoplasm* or tumor* or tumour* or malignan* or carcin* or polyp* or oncolog* or sarcoma* or adenocarcin*)):ti,ab,kw 20322

#16 #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 43979

#17 ((plastic* or flexib* or retract* or stretch* or soft or novel) near/5 (tip or tips or cuff or cuffs or cap or caps or attachment* or accessor* or device* or hinge*)):ti,ab,kw 811

#18 ((plastic* or flexib* or retract* or stretch* or invert* or evert* or soft or hinge*) near/5 (finger* or branch* or arm or arms or projection* or flange*)):ti,ab,kw 163

#19 ((assisted or assistive) near/5 (tip or tips or cuff or cuffs or cap or caps or attachment* or accessor* or device*)):ti,ab,kw 395

#20 #17 or #18 or #19 1349

#21 #16 and #20 130

#22 ((colonoscop* or endoscop* or sigmoidoscop*) and (tip or tips or cuff or cuffs or cap or caps or attachment* or accessor*)):ti 88

#23 ((colonoscop* or endoscop* or sigmoidoscop*) near/5 (tip or tips or cuff or cuffs or cap or caps or attachment* or accessor*)):ab,kw 118

#24 #6 or #21 or #22 or #23 Online Publication Date from Jan 2010 to Jan 2017, in Cochrane Reviews (Reviews and Protocols) 8

Conference Proceedings Citation Index – Science (CPCI-S)

URL/Interface: Web of Knowledge/Thomson Reuters

Database coverage dates: 1990-current

Search date: 11 January 2017

Records retrieved: 275

Search strategy:

18

275

#6 OR #15 OR #16 OR #17

Indexes=CPCI-S Timespan=2010-2017

17

71

TS=((colonoscop* OR endoscop* OR sigmoidoscop*) NEAR/5 ("tip" OR "tips" OR "cuff" OR "cuffs" OR "cap" OR "caps" OR attachment* OR accessor*))

Indexes=CPCI-S Timespan=2010-2017

16

38

TI=((colonoscop* OR endoscop* OR sigmoidoscop*) AND ("tip" OR "tips" OR "cuff" OR "cuffs" OR "cap" OR "caps" OR attachment* OR accessor*))

15

145

#10 AND #14

Indexes=CPCI-S Timespan=2010-2017

14

6,727

#11 OR #12 OR #13

Indexes=CPCI-S Timespan=2010-2017

13

772

TS=(("assisted" OR "assistive") NEAR/5 ("tip" OR "tips" OR "cuff" OR "cuffs" OR "cap" OR "caps" OR attachment* OR accessor* OR device$))

Indexes=CPCI-S Timespan=2010-2017

12

658

TS=((plastic* OR flexib* OR retract* OR stretch* OR invert* OR evert* OR "soft" OR hinge$) NEAR/5 (finger$ OR branch* OR "arm" OR "arms" OR projection$ OR flange$))

Indexes=CPCI-S Timespan=2010-2017

11

5,377

TS=((plastic* OR flexib* OR retract* OR stretch* OR "soft" OR "novel") NEAR/5 ("tip" OR "tips" OR "cuff" OR "cuffs" OR "cap" OR "caps" OR attachment* OR accessor* OR device$ OR hinge$))

Indexes=CPCI-S Timespan=2010-2017

10

45,951

#7 OR #8 OR #9

Indexes=CPCI-S Timespan=2010-2017

9

19,004

TS=((bowel$ OR intestin* OR colorectal* OR colon* OR rectum* OR rectal* OR anal* OR "anus" OR sigmoid*) NEAR/3 (cancer* OR neoplasm* OR tumor* OR tumour* OR malignan* OR carcin* OR polyp* OR oncolog* OR sarcoma* OR adenocarcin*))

Indexes=CPCI-S Timespan=2010-2017

8

20,424

TS=((bowel$ OR intestin* OR colorectal* OR colon* OR rectum* OR rectal* OR anal* OR "anus" OR sigmoid*) NEAR/3 (screen* OR investigat* OR diagnos* OR detect*))

Indexes=CPCI-S Timespan=2010-2017

7

9,323

TS=(colonoscop* OR endoscop* OR sigmoidoscop*)

6

76

#1 OR #2 OR #3 OR #4 OR #5

Indexes=CPCI-S Timespan=2010-2017

5

67

OG=(arc NEAR/0 medical* OR arcmedical* OR arc NEAR/0 design* OR arcdesign* OR norgine*) OR AD=(arc NEAR/0 medical* OR arcmedical* OR arc NEAR/0 design* OR arcdesign* OR norgine*) OR SG=(arc NEAR/0 medical* OR arcmedical* OR arc NEAR/0 design* OR arcdesign* or norgine*) OR FO=(arc NEAR/0 medical* OR arcmedical* OR arc NEAR/0 design* OR arcdesign* OR norgine*) OR TS=(arc NEAR/0 medical* OR arcmedical* OR arc NEAR/0 design* OR arcdesign* OR norgine*)

Indexes=CPCI-S Timespan=2010-2017

4

0

TS=("aec-110" OR "aec-120" OR "aec-130" OR "aec-140")

Indexes=CPCI-S Timespan=2010-2017

3

0

TS=("aec110" OR "aec120" OR "aec130" OR "aec140")

Indexes=CPCI-S Timespan=2010-2017

2

2

TS="ec-assisted"

Indexes=CPCI-S Timespan=2010-2017

1

7

TS=(endocuff* or endo-cuff* or ecvision* or ec-vision*)

Indexes=CPCI-S Timespan=2010-2017

WHO International Clinical Trials Registry Portal (ICTRP)

URL/Interface: http://apps.who.int/trialsearch/

Database coverage dates: not indicated

Search date: 11 January 2017

Records retrieved: 17

Search strategy:

The default search screen was used.

endocuff OR endo-cuff OR ecvision OR ec-vision OR ec-assisted OR aec110 OR aec120 OR aec130 OR aec140 OR aec-110 OR aec-120 OR aec-130 OR aec-140

The 17 records retrieved by the update search were checked by hand against the 17 records retrieved by the original search and were found to be identical. Due to database functionality problems the 17 records retrieved by the update search were not downloaded and as such are not accounted for in the PRISMA flow diagram.

ClinicalTrials.gov

URL/Interface: https://clinicaltrials.gov./

Database coverage dates: not indicated

Search date: 11 January 2017

Records retrieved: 13

Search strategy:

The “Advanced Search” screen was used. Terms were searched using the “Search Terms” field.

endocuff OR endo-cuff OR ecvision OR ec-vision OR ec-assisted OR aec110 OR aec120 OR aec130 OR aec140 OR aec-110 OR aec-120 OR aec-130 OR aec-140

UK Clinical Trials Gateway

URL/Interface: https://www.ukctg.nihr.ac.uk/

Database coverage dates: not indicated

Search date: 11 January 2017

Records retrieved: 4

Only a basic search option is available. Truncation seems to be automatic. Use of Boolean operators is not allowed. The system seems to perform an implicit “AND” operation if two or more terms are used.

All statuses were selected from “Trial Status” option on the result page.

endocuff 4 results

endo-cuff: 1 result (the same record was found by endocuff and was not downloaded)

ecvision no results

ec-vision: no results

ec-assisted: no results

aec110: no results

aec120: no results

aec130: no results

aec140: no results

aec-110: no results

aec-120: no results

aec-130: no results

aec-140: no results

Cost Effectiveness Analysis Registry (CEA Registry)

Interface/URL: http://healtheconomics.tuftsmedicalcenter.org/cear4/Home.aspx

Database coverage dates: 1976 to current

Search date: 11 January 2017

Records retrieved: 0

Search strategy:

Basic search option was used. Only single terms are permitted, therefore each term was searched for separately.

endocuff: no results

endo-cuff: no results

ecvision no results

ec-vision: no results

aec110: no results

aec120: no results

aec130: no results

aec140: no results

aec-110: no results

aec-120: no results

aec-130: no results

aec-140: no results

U.S. Food and Drug Administration (FDA)

Interface/URL: http://www.fda.gov/

Database coverage dates: not indicated

Search date: 11 January 2017

Records retrieved: 14

Search strategy:

Site wide search functionality was used.

endocuff: 14 results

endo-cuff: 1 result, included in 14 results found by “endocuff”

ecvision no results

ec-vision: no results

ec-assisted: no results

aec110: 1 result, included in 14 results found by “endocuff”

aec120: 1 result, included in 14 results found by “endocuff”

aec130: 1 result, included in 14 results found by “endocuff”

aec140: 1 result, included in 14 results found by “endocuff”

aec-110: 4 results, included in 14 results found by “endocuff”

aec-120: 4 results, included in 14 results found by “endocuff”

aec-130: 1 result, included in 14 results found by “endocuff”

aec-140: 4 results, included in 14 results found by “endocuff”

American College of Gastroenterology Annual Scientific Meeting 2016

Interface/URL:

http://acgmeetings.gi.org/

https://www.eventscribe.com/2016/ACG/SearchPostersByKeyword.asp# (Poster search)

https://www.eventscribe.com/2016/ACG/SearchByKeyword.asp (Courses/Session search)

Search date: 28 November 2016

Records retrieved: 1

Search strategy: see below

Keywords were searched individually. It was not possible to use truncation. Use of Boolean operators was not possible.

Poster search:

endocuff: 1 result

endo-cuff: no results

ecvision: no results

ec-vision: no results

ec-assisted: results

aec110: no results

aec120: no results

aec130: no results

aec140: no results

aec-110: no results

aec-120: no results

aec-130: no results

aec-140: no results

Courses/Session search:

endocuff: no results

endo-cuff: no results

ecvision: no results

ec-vision: no results

ec-assisted: results

aec110: no results

aec120: no results

aec130: no results

aec140: no results

aec-110: no results

aec-120: no results

aec-130: no results

aec-140: no results

United European Gastroenterology Week 2016

Interface/URL:

https://www.ueg.eu/week/

https://www.ueg.eu/education/library/#stq=%20&stp=1?abstract2016=true

Search date: 28 November 2016

Records retrieved: 6

Search strategy: see below

Keywords were searched individually. Truncation seemed automatic. Hyphenated words and terms containing both numbers and words needed to be encased in quotation marks to increase precision (words appearing together rather than anywhere in the document separately). It was not possible to use Boolean operators.

endocuff: 6 results

“endo-cuff”: no results

ecvision: no results

“ec-vision”: no results

“ec-assisted”: no results

“aec110”: no results

“aec120”: no results

“aec130”: no results

“aec140”: no results

“aec-110”: no results

“aec-120”: no results

“aec-130”: no results

“aec-140”: no results

British Society of Gastroenterology Annual Meeting 2015 and 2016

Interface/URL:

http://www.bsg.org.uk/education/meeting/index.html

http://www.bsg.org.uk/images/stories/docs/bsg_abstracts_16.pdf

http://www.bsg.org.uk/images/stories/docs/education/bsg_abstracts_15.pdf

Search date: 2 December 2016

Records retrieved: 3

Search strategy: see below

Abstract books for the annual meetings were searched using ctrl+f

endocuff: 3 results

endo-cuff: no results

ecvision: no results

ec-vision: no results

ec-assisted: results

aec110: no results

aec120: no results

aec130: no results

aec140: no results

aec-110: no results

aec-120: no results

aec-130: no results

aec-140: no results

Details of the Update search – February 2018)

Database / information source	Number of records downloaded
MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE Daily and MEDLINE	1,129
Embase	2,696
EconLit	0
Cochrane Database of Systematic Reviews (CDSR)	10
Cochrane Central Register of Controlled Trials (CENTRAL)	434
Health Technology Assessment Database (HTA Database)	0
Conference Proceedings Citation Index – Science (CPCI)	385
WHO International Clinical Trials Registry Portal (ICTRP)	28
ClinicalTrials.gov	20
UK Clinical Trials Gateway	9
Cost Effectiveness Analysis Registry (CEA Registry)	0
U.S. Food and Drug Administration (FDA) webpage	9
Digestive Disease Week 2017	9
American College of Gastroenterology Annual Scientific Meeting 2017	11
British Society of Gastroenterology Annual Meeting 2017	0
United European Gastroenterology Week 2017	2
Records identified via other methods	0
Total number of records identified	4,742

The searches of NHS EED and DARE were not updated as these resources closed to new records in 2015. No new records could have been added since the original search.

Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Interface / URL: OvidSP

Database coverage dates: 1946 to present

Search date: 06/02/18

Retrieved records: 1,129

Search strategy:

1 (endocuff$ or endo-cuff$ or ecvision$ or ec-vision$).ti,ab,kf. (30)

2 ec-assisted.ti,ab,kf. (5)

3 (aec110 or aec120 or aec130 or aec140).ti,ab,kf. (0)

4 (aec-110 or aec-120 or aec-130 or aec-140).ti,ab,kf. (0)

5 (arc medical$ or arcmedical$ or arc design$ or arcdesign$ or norgine$).ti,ab,kf,in. (42)

6 or/1-5 (72)

7 Endoscopes, Gastrointestinal/ (1628)

8 exp Colonoscopes/ (1250)

9 Endoscopy, Gastrointestinal/ (16762)

10 exp Colonoscopy/ (26409)

11 exp Colorectal Neoplasms/ (177459)

12 Colonic Polyps/ (7495)

13 (colonoscop$ or endoscop$ or sigmoidoscop$).ti,ab,kf. (199938)

14 ((bowel$1 or intestin$ or colorectal$ or colon$ or rectum$ or rectal$ or anal$ or anus or sigmoid$) adj3 (screen$ or investigat$ or diagnos$ or detect$)).ti,ab,kf. (145275)

15 ((bowel$1 or intestin$ or colorectal$ or colon$ or rectum$ or rectal$ or anal$ or anus or sigmoid$) adj3 (cancer$ or neoplasm$ or tumor$ or tumour$ or malignan$ or carcin$ or polyp$ or oncolog$ or sarcoma$ or adenocarcin$)).ti,ab,kf. (288408)

16 or/7-15 (625068)

17 ((plastic$ or flexib$ or retract$ or stretch$ or soft or novel) adj5 (tip or tips or cuff or cuffs or cap or caps or attachment$ or accessor$ or device$1 or hinge$1)).ti,ab,kf. (16179)

18 ((plastic$ or flexib$ or retract$ or stretch$ or invert$ or evert$ or soft or hinge$1) adj5 (finger$1 or branch$ or arm or arms or projection$1 or flange$1)).ti,ab,kf. (3098)

19 ((assisted or assistive) adj5 (tip or tips or cuff or cuffs or cap or caps or attachment$ or accessor$ or device$1)).ti,ab,kf. (4119)

20 or/17-19 (23169)

21 16 and 20 (1118)

22 ((colonoscop$ or endoscop$ or sigmoidoscop$) and (tip or tips or cuff or cuffs or cap or caps or attachment$ or accessor$)).ti. (425)

23 ((colonoscop$ or endoscop$ or sigmoidoscop$) adj5 (tip or tips or cuff or cuffs or cap or caps or attachment$ or accessor$)).ab,kf. (1033)

24 6 or 21 or 22 or 23 (2265)

25 exp animals/ not humans/ (4421613)

26 24 not 25 (2078)

27 limit 26 to yr="2010 -Current" (1130)

28 remove duplicates from 27 (1129)

Embase 1974 to 2018 February 05

Interface / URL: OvidSP

Database coverage dates: 1974 to 2018 February 05

Search date: 06/02/18

Retrieved records: 2696

Search strategy:

1 (endocuff$ or endo-cuff$ or ecvision$ or ec-vision$).ti,ab,kw,dv. (89)

2 ec-assisted.ti,ab,kw,dv. (12)

3 (aec110 or aec120 or aec130 or aec140).ti,ab,kw,dv. (3)

4 (aec-110 or aec-120 or aec-130 or aec-140).ti,ab,kw,dv. (0)

5 (arc medical$ or arcmedical$ or arc design$ or arcdesign$ or norgine$).ti,ab,kw,in,dm. (224)

6 or/1-5 (296)

7 digestive endoscope/ (851)

8 exp sigmoidoscope/ (313)

9 exp colonoscope/ (2841)

10 gastrointestinal endoscopy/ (28893)

11 colonoscopy/ (64541)

12 sigmoidoscopy/ (11146)

13 exp rectum tumor/ (212040)

14 exp colon tumor/ (273299)

15 exp colon polyp/ (17694)

16 (colonoscop$ or endoscop$ or sigmoidoscop$).ti,ab,kw. (306845)

17 ((bowel$1 or intestin$ or colorectal$ or colon$ or rectum$ or rectal$ or anal$ or anus or sigmoid$) adj3 (screen$ or investigat$ or diagnos$ or detect$)).ti,ab,kw. (200835)

18 ((bowel$1 or intestin$ or colorectal$ or colon$ or rectum$ or rectal$ or anal$ or anus or sigmoid$) adj3 (cancer$ or neoplasm$ or tumor$ or tumour$ or malignan$ or carcin$ or polyp$ or oncolog$ or sarcoma$ or adenocarcin$)).ti,ab,kw. (405448)

19 or/7-18 (918835)

20 ((plastic$ or flexib$ or retract$ or stretch$ or soft or novel) adj5 (tip or tips or cuff or cuffs or cap or caps or attachment$ or accessor$ or device$1 or hinge$1)).ti,ab,kw. (18552)

21 ((plastic$ or flexib$ or retract$ or stretch$ or invert$ or evert$ or soft or hinge$1) adj5 (finger$1 or branch$ or arm or arms or projection$1 or flange$1)).ti,ab,kw. (3664)

22 ((assisted or assistive) adj5 (tip or tips or cuff or cuffs or cap or caps or attachment$ or accessor$ or device$1)).ti,ab,kw. (5773)

23 or/20-22 (27663)

24 19 and 23 (2160)

25 ((colonoscop$ or endoscop$ or sigmoidoscop$) and (tip or tips or cuff or cuffs or cap or caps or attachment$ or accessor$)).ti. (652)

26 ((colonoscop$ or endoscop$ or sigmoidoscop$) adj5 (tip or tips or cuff or cuffs or cap or caps or attachment$ or accessor$)).ab,kw. (1911)

27 6 or 24 or 25 or 26 (4239)

28 (animal/ or animal experiment/ or animal model/ or animal tissue/ or nonhuman/) not exp human/ (5788515)

29 27 not 28 (3940)

30 limit 29 to yr="2010 -Current" (2743)

31 remove duplicates from 30 (2696)

Econlit

Interface / URL: OvidSP

Database coverage dates: 1886 to December 2017

Search date: 06/02/18

Retrieved records: 0

Search strategy:

1 (endocuff$ or endo-cuff$ or ecvision$ or ec-vision$).ti,ab,kw. (1)

2 ec-assisted.ti,ab,kw. (0)

3 (aec110 or aec120 or aec130 or aec140).ti,ab,kw. (0)

4 (aec-110 or aec-120 or aec-130 or aec-140).ti,ab,kw. (0)

5 (arc medical$ or arcmedical$ or arc design$ or arcdesign$ or norgine$).ti,ab,kw,in. (1)

6 or/1-5 (2)

7 (colonoscop$ or endoscop$ or sigmoidoscop$).ti,ab,kw. (44)

8 ((bowel$1 or intestin$ or colorectal$ or colon$ or rectum$ or rectal$ or anal$ or anus or sigmoid$) adj3 (screen$ or investigat$ or diagnos$ or detect$)).ti,ab,kw. (1892)

9 ((bowel$1 or intestin$ or colorectal$ or colon$ or rectum$ or rectal$ or anal$ or anus or sigmoid$) adj3 (cancer$ or neoplasm$ or tumor$ or tumour$ or malignan$ or carcin$ or polyp$ or oncolog$ or sarcoma$ or adenocarcin$)).ti,ab,kw. (173)

10 or/7-9 (2042)

11 ((plastic$ or flexib$ or retract$ or stretch$ or soft or novel) adj5 (tip or tips or cuff or cuffs or cap or caps or attachment$ or accessor$ or device$1 or hinge$1)).ti,ab,kw. (61)

12 ((plastic$ or flexib$ or retract$ or stretch$ or invert$ or evert$ or soft or hinge$1) adj5 (finger$1 or branch$ or arm or arms or projection$1 or flange$1)).ti,ab,kw. (22)

13 ((assisted or assistive) adj5 (tip or tips or cuff or cuffs or cap or caps or attachment$ or accessor$ or device$1)).ti,ab,kw. (15)

14 or/11-13 (97)

15 10 and 14 (0)

16 ((colonoscop$ or endoscop$ or sigmoidoscop$) and (tip or tips or cuff or cuffs or cap or caps or attachment$ or accessor$)).ti. (0)

17 ((colonoscop$ or endoscop$ or sigmoidoscop$) adj5 (tip or tips or cuff or cuffs or cap or caps or attachment$ or accessor$)).ab,kw. (0)

18 6 or 15 or 16 or 17 (2)

19 limit 18 to yr="2010-current" (0)

Cochrane Database of Systematic Reviews (CDSR)

Interface / URL: Wiley Cochrane Library

Database coverage dates: Issue 2 of 12, February 2018

Search date: 07/02/18

Retrieved records: 10

Search strategy:

#1	(endocuff* or endo-cuff* or ecvision* or ec-vision*):ti,ab,kw	27
#2	ec-assisted:ti,ab,kw	5
#3	(aec110 or aec120 or aec130 or aec140):ti,ab,kw	0
#4	(aec-110 or aec-120 or aec-130 or aec-140):ti,ab,kw	0
#5	(arc next medical* or arcmedical* or arc next design* or arcdesign* or norgine*):ti,ab,kw	11
#6	#1 or #2 or #3 or #4 or #5	34
#7	MeSH descriptor: [Endoscopes, Gastrointestinal] this term only	65
#8	MeSH descriptor: [Colonoscopes] explode all trees	138
#9	MeSH descriptor: [Endoscopy, Gastrointestinal] this term only	899
#10	MeSH descriptor: [Colonoscopy] explode all trees	2019
#11	MeSH descriptor: [Colorectal Neoplasms] explode all trees	6626
#12	MeSH descriptor: [Colonic Polyps] this term only	390
#13	(colonoscop* or endoscop* or sigmoidoscop*):ti,ab,kw	21129
#14	((bowel* or intestin* or colorectal* or colon* or rectum* or rectal* or anal* or anus or sigmoid*) near/3 (screen* or investigat* or diagnos* or detect*)):ti,ab,kw	14317
#15	((bowel* or intestin* or colorectal* or colon* or rectum* or rectal* or anal* or anus or sigmoid*) near/3 (cancer* or neoplasm* or tumor* or tumour* or malignan* or carcin* or polyp* or oncolog* or sarcoma* or adenocarcin*)):ti,ab,kw	25330
#16	#7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15	53812

#17 ((plastic* or flexib* or retract* or stretch* or soft or novel) near/5 (tip or tips or cuff or cuffs or cap or caps or attachment* or accessor* or device* or hinge*)):ti,ab,kw 1104

#18 ((plastic* or flexib* or retract* or stretch* or invert* or evert* or soft or hinge*) near/5 (finger* or branch* or arm or arms or projection* or flange*)):ti,ab,kw 206

#19 ((assisted or assistive) near/5 (tip or tips or cuff or cuffs or cap or caps or attachment* or accessor* or device*)):ti,ab,kw 549

#20 #17 or #18 or #19 1822

#21 #16 and #20 217

#22 ((colonoscop* or endoscop* or sigmoidoscop*) and (tip or tips or cuff or cuffs or cap or caps or attachment* or accessor*)):ti 110

#23 ((colonoscop* or endoscop* or sigmoidoscop*) near/5 (tip or tips or cuff or cuffs or cap or caps or attachment* or accessor*)):ab,kw 163

#24 #6 or #21 or #22 or #23 Online Publication Date from Jan 2010 to Feb 2018, in Cochrane Reviews (Reviews and Protocols) 10

Cochrane Central Register of Controlled Trials (CENTRAL)

Interface / URL: Wiley Cochrane Library

Database coverage dates: Issue 1 of 12, January 2018

Search date: 07/02/18

Retrieved records: 434

Search strategy:

#1 (endocuff* or endo-cuff* or ecvision* or ec-vision*) 29

#2 ec-assisted 5

#3 (aec110 or aec120 or aec130 or aec140) 0

#4 (aec-110 or aec-120 or aec-130 or aec-140) 0

#5 (arc next medical* or arcmedical* or arc next design* or arcdesign* or norgine*) 57

#6 #1 or #2 or #3 or #4 or #5 82

#7 MeSH descriptor: [Endoscopes, Gastrointestinal] this term only 65

#8 MeSH descriptor: [Colonoscopes] explode all trees 138

#9 MeSH descriptor: [Endoscopy, Gastrointestinal] this term only 899

#10 MeSH descriptor: [Colonoscopy] explode all trees 2019

#11 MeSH descriptor: [Colorectal Neoplasms] explode all trees 6626

#12 MeSH descriptor: [Colonic Polyps] this term only 390

#13 (colonoscop* or endoscop* or sigmoidoscop*) 24652

#14 ((bowel* or intestin* or colorectal* or colon* or rectum* or rectal* or anal* or anus or sigmoid*) near/3 (screen* or investigat* or diagnos* or detect*)) 23417

#15 ((bowel* or intestin* or colorectal* or colon* or rectum* or rectal* or anal* or anus or sigmoid*) near/3 (cancer* or neoplasm* or tumor* or tumour* or malignan* or carcin* or polyp* or oncolog* or sarcoma* or adenocarcin*)) 26711

#16 #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 65455

#17 ((plastic* or flexib* or retract* or stretch* or soft or novel) near/5 (tip or tips or cuff or cuffs or cap or caps or attachment* or accessor* or device* or hinge*)) 1229

#18 ((plastic* or flexib* or retract* or stretch* or invert* or evert* or soft or hinge*) near/5 (finger* or branch* or arm or arms or projection* or flange*)) 296

#19 ((assisted or assistive) near/5 (tip or tips or cuff or cuffs or cap or caps or attachment* or accessor* or device*)) 716

#20 #17 or #18 or #19 2171

#21 #16 and #20 475

#22 ((colonoscop* or endoscop* or sigmoidoscop*) and (tip or tips or cuff or cuffs or cap or caps or attachment* or accessor*)) 674

#23 ((colonoscop* or endoscop* or sigmoidoscop*) near/5 (tip or tips or cuff or cuffs or cap or caps or attachment* or accessor*)) 225

#24 #6 or #21 or #22 or #23 Publication Year from 2010 to 2018, in Trials 434

Health Technology Assessment database

Interface / URL: https://www.crd.york.ac.uk/CRDWeb/HomePage.asp

Database coverage dates: Not found

Search date: 06/02/18

Retrieved records: 0

Search strategy:

1 ((endocuff* or endo-cuff* or ecvision* or ec-vision*)) 0

2 (ec-assisted) 0

3 ((aec110 or aec120 or aec130 or aec140)) 0

4 ((aec-110 or aec-120 or aec-130 or aec-140)) 0

5	((arc medical* or arcmedical* or arc design* or arcdesign* or norgine*))	5
6	#1 OR #2 OR #3 OR #4 OR #5	5
7	MeSH DESCRIPTOR Endoscopes, Gastrointestinal	12
8	MeSH DESCRIPTOR Colonoscopes EXPLODE ALL TREES	12
9	MeSH DESCRIPTOR Endoscopy, Gastrointestinal	169
10	MeSH DESCRIPTOR Colonoscopy EXPLODE ALL TREES	289
11	MeSH DESCRIPTOR Colorectal Neoplasms EXPLODE ALL TREES	1436
12	MeSH DESCRIPTOR Colonic Polyps	69
13	((colonoscop* or endoscop* or sigmoidoscop*))	2369
14	(((bowel* or intestin* or colorectal* or colon* or rectum* or rectal* or anal* or anus or sigmoid*) near3 (screen* or investigat* or diagnos* or detect*)))	3442
15	(((bowel* or intestin* or colorectal* or colon* or rectum* or rectal* or anal* or anus or sigmoid*) near3 (cancer* or neoplasm* or tumor* or tumour* or malignan* or carcin* or polyp* or oncolog* or sarcoma* or adenocarcin*)))	2539
16	#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15	7006
17	(((plastic* or flexib* or retract* or stretch* or soft or novel) near5 (tip or tips or cuff or cuffs or cap or caps or attachment* or accessor* or device* or hinge*)))	24
18	(((plastic* or flexib* or retract* or stretch* or invert* or evert* or soft or hinge*) near5 (finger* or branch* or arm or arms or projection* or flange*)))	4

19 (((assisted or assistive) near5 (tip or tips or cuff or cuffs or cap or caps or attachment* or accessor* or device*))) 53

20 #17 OR #18 OR #19 81

21 #16 AND #20 7

22 (((colonoscop* or endoscop* or sigmoidoscop*) and (tip or tips or cuff or cuffs or cap or caps or attachment* or accessor*))):TI 9

23 (((colonoscop* or endoscop* or sigmoidoscop*) near5 (tip or tips or cuff or cuffs or cap or caps or attachment* or accessor*))) 10

24 #6 OR #21 OR #22 OR #23 25

25 (#24) FROM 2010 TO 2018 12

26 (#25) IN HTA FROM 2010 TO 2018 0

Conference Proceedings Citation Index – Science (CPCI)

Interface / URL: Clarivate Analytics/Web of Science

Database coverage dates: 1990-current

Search date: 07/02/18

Retrieved records: 385

Search strategy:

18

385

#6 OR #15 OR #16 OR #17

Indexes=CPCI-S Timespan=2010-2018

17

95

TS=((colonoscop* OR endoscop* OR sigmoidoscop*) NEAR/5 ("tip" OR "tips" OR "cuff" OR "cuffs" OR "cap" OR "caps" OR attachment* OR accessor*))

Indexes=CPCI-S Timespan=2010-2018

16

66

TI=((colonoscop* OR endoscop* OR sigmoidoscop*) AND ("tip" OR "tips" OR "cuff" OR "cuffs" OR "cap" OR "caps" OR attachment* OR accessor*))

Indexes=CPCI-S Timespan=2010-2018

15

192

#10 AND #14

Indexes=CPCI-S Timespan=2010-2018

14

8,664

#11 OR #12 OR #13

Indexes=CPCI-S Timespan=2010-2018

13

1,053

TS=(("assisted" OR "assistive") NEAR/5 ("tip" OR "tips" OR "cuff" OR "cuffs" OR "cap" OR "caps" OR attachment* OR accessor* OR device$))

Indexes=CPCI-S Timespan=2010-2018

12

877

TS=((plastic* OR flexib* OR retract* OR stretch* OR invert* OR evert* OR "soft" OR hinge$) NEAR/5 (finger$ OR branch* OR "arm" OR "arms" OR projection$ OR flange$))

Indexes=CPCI-S Timespan=2010-2018

11

6,835

TS=((plastic* OR flexib* OR retract* OR stretch* OR "soft" OR "novel") NEAR/5 ("tip" OR "tips" OR "cuff" OR "cuffs" OR "cap" OR "caps" OR attachment* OR accessor* OR device$ OR hinge$))

Indexes=CPCI-S Timespan=2010-2018

10

59,992

#7 OR #8 OR #9

Indexes=CPCI-S Timespan=2010-2018

9

24,412

TS=((bowel$ OR intestin* OR colorectal* OR colon* OR rectum* OR rectal* OR anal* OR "anus" OR sigmoid*) NEAR/3 (cancer* OR neoplasm* OR tumor* OR tumour* OR malignan* OR carcin* OR polyp* OR oncolog* OR sarcoma* OR adenocarcin*))

Indexes=CPCI-S Timespan=2010-2018

8

26,297

TS=((bowel$ OR intestin* OR colorectal* OR colon* OR rectum* OR rectal* OR anal* OR "anus" OR sigmoid*) NEAR/3 (screen* OR investigat* OR diagnos* OR detect*))

Indexes=CPCI-S Timespan=2010-2018

7

12,937

TS=(colonoscop* OR endoscop* OR sigmoidoscop*)

Indexes=CPCI-S Timespan=2010-2018

6

119

#1 OR #2 OR #3 OR #4 OR #5

Indexes=CPCI-S Timespan=2010-2018

5

93

OG=(arc NEAR/0 medical* OR arcmedical* OR arc NEAR/0 design* OR arcdesign* OR norgine*) OR AD=(arc NEAR/0 medical* OR arcmedical* OR arc NEAR/0 design* OR arcdesign* OR norgine*) OR SG=(arc NEAR/0 medical* OR arcmedical* OR arc NEAR/0 design* OR arcdesign* or norgine*) OR FO=(arc NEAR/0 medical* OR arcmedical* OR arc NEAR/0 design* OR arcdesign* OR norgine*) OR TS=(arc NEAR/0 medical* OR arcmedical* OR arc NEAR/0 design* OR arcdesign* OR norgine*)

Indexes=CPCI-S Timespan=2010-2018

4

0

TS=("aec-110" OR "aec-120" OR "aec-130" OR "aec-140")

Indexes=CPCI-S Timespan=2010-2018

3

0

TS=("aec110" OR "aec120" OR "aec130" OR "aec140")

Indexes=CPCI-S Timespan=2010-2018

2

3

TS="ec-assisted"

Indexes=CPCI-S Timespan=2010-2018

1

24

TS=(endocuff* or endo-cuff* or ecvision* or ec-vision*)

Indexes=CPCI-S Timespan=2010-2018

WHO International Clinical Trials Registry Portal (ICTRP)

Interface / URL: http://apps.who.int/trialsearch/

Database coverage dates: Not indicated

Search date: 06/02/18

Retrieved records: 28

Search strategy:

The default search screen was used:

endocuff OR endo-cuff OR ecvision OR ec-vision OR ec-assisted OR aec110 OR aec120 OR aec130 OR aec140 OR aec-110 OR aec-120 OR aec-130 OR aec-140 28 records found for 28 trials

ClinicalTrials.gov

Interface / URL: https://clinicaltrials.gov./

Database coverage dates: Not indicated

Search date: 06/02/18

Retrieved records: 20

Search strategy:

The Expert search screen was used:

endocuff OR endo-cuff OR ecvision OR ec-vision OR ec-assisted OR aec110 OR aec120 OR aec130 OR aec140 OR aec-110 OR aec-120 OR aec-130 OR aec-140 20 studies found

UK Clinical Trials Gateway

Interface / URL: https://www.ukctg.nihr.ac.uk/home/

Database coverage dates: Not indicated

Search date: 06/02/18

Retrieved records: 9

Search strategy:

Only a basic search option is available. Use of Boolean operators is not allowed. The system seems to perform an implicit “AND” operation if two or more terms are used.

All statuses were selected from “Trial Status” option on the result page.

endocuff*: 9 results

endo-cuff*: 0 results

ecvision*: 0 results

ec-vision*: 0 results

ec-assisted*: 0 results

aec110*: 0 results

aec120*: 0 results

aec130*: 0 results

aec140*: 0 results

aec-110*: 0 results

aec-120*: 0 results

aec-130*: 0 results

aec-140*: 0 results

Cost Effectiveness Analysis Registry (CEA Registry)

Interface / URL: http://healtheconomics.tuftsmedicalcenter.org/cear4/Home.aspx

Database coverage dates: 1976 to current

Search date: 06/02/18

Retrieved records: 0

Search strategy:

Search conducted using the basic search option. Very basic search interface; no Boolean, truncation etc. supported.

endocuff: no results

endo-cuff: no results

ecvision no results

ec-vision: no results

aec110: no results

aec120: no results

aec130: no results

aec140: no results

aec-110: no results

aec-120: no results

aec-130: no results

aec-140: no results

U.S. Food and Drug Administration (FDA) webpage

Interface / URL: https://www.fda.gov/

Database coverage dates: N/A

Search date: 06/02/18

Retrieved records: 9

Search strategy:

Site wide search functionality was used:

endocuff: 9 results

endo-cuff: 9 results (identical to above – not downloaded)

ecvision 0 results

ec-vision: 0 results

ec-assisted: 0 results

aec110: 1 result (already identified above – not downloaded)

aec120: 1 result (already identified above – not downloaded)

aec130: 1 result (already identified above – not downloaded)

aec140: 1 result (already identified above – not downloaded)

aec-110: 4 results (already identified above – not downloaded)

aec-120: 4 results (already identified above – not downloaded)

aec-130: 1 result (already identified above – not downloaded)

aec-140: 4 results (already identified above – not downloaded)

Digestive Disease Week 2017

Interface / URL:

Database coverage dates: n/a

Search date: 22/02/18

Retrieved records: 9

Search strategy:

Abstracts accepted for presentation at DDW 2017 are in the April 2017 supplement to Gastroenterology (http://www.ddw.org/ddwwebsite/education/abstracts)

The following supplement was searched: April 2017 Volume 152, Issue 5, Supplement 1, S1-S1316 (http://www.gastrojournal.org/issue/S0016-5085(17)X5200-1).

The ‘Search within this issue’ function was used. The following terms were searched individually across ‘all content’:

endocuff: 2 results

"endo-cuff": 0 results

ecvision: 0 results

"ec-vision": 0 results

"ec-assisted": 0 results

aec110: 0 results

aec120: 0 results

aec130: 0 results

aec140: 0 results

"aec-110": 0 results

"aec-120": 0 results

"aec-130": 0 results

"aec-140": 0 results

Abstracts accepted for presentation at DDW 2017 also appear to be in the May 2017 supplement to Gastrointestinal Endoscopy Vol 85 Issue 5
http://www.giejournal.org/issue/S0016-5107(17)X0005-9

The ‘Search within this issue’ function was used. The following terms were searched individually across ‘all content’. Results were limited to articles.

endocuff: 7 results

"endo-cuff": 0 results

ecvision: 0 results

"ec-vision": 0 results

"ec-assisted": 0 results

aec110: 0 results

aec120: 0 results

aec130: 0 results

aec140: 0 results

"aec-110": 0 results

"aec-120": 0 results

"aec-130": 0 results

"aec-140": 0 results

American College of Gastroenterology Annual Scientific Meeting 2017

Interface / URL: https://www.eventscribe.com/2017/wcogacg2017/

Database coverage dates: n/a

Search date: 22/02/18

Retrieved records: 11 records (7 unique records, 4 duplicates)

Search strategy:

Search 1. The Courses/Sessions were searched using the Keyword Search option at: https://www.eventscribe.com/2017/wcogacg2017/search.asp.

The following terms were searched individually:

endocuff: 3 results

endo-cuff: 0 results

ecvision: 0 results

ec-vision: 0 results

ec-assisted: 0 results

aec110: 0 results

aec120: 0 results

aec130: 0 results

aec140: 0 results

aec-110: 0 results

aec-120: 0 results

aec-130: 0 results

aec-140: 0 results

Search 2. The Posters were searched using the Browse by title option, filtered with the following terms searched on individually:

endocuff: 2 results

endo-cuff: 0 results

ecvision: 0 results

ec-vision: 0 results

ec-assisted: 0 results

aec110: 0 results

aec120: 0 results

aec130: 0 results

aec140: 0 results

aec-110: 0 results

aec-120: 0 results

aec-130: 0 results

aec-140: 0 results

Search 3. The abstracts were searched using control + f option at: http://www.nature.com/ajg/journal/v112/n1s/index.html

Topic-specific pdf files were searched separately.

Meeting Abstracts:

Biliary/Pancreas

Colon

Endoscopy video forum

Esophagus

Functional bowel disease

General endoscopy

GI bleeding

Inflammatory bowel disease

Interventional endoscopy

Liver

Obesity

Pediatrics

Small intestine

Stomach

endocuff: 0 results

endo-cuff: 0 results

ecvision: 0 results

ec-vision: 0 results

ec-assisted: 0 results

aec110: 0 results

aec120: 0 results

aec130: 0 results

aec140: 0 results

aec-110: 0 results

aec-120: 0 results

aec-130: 0 results

aec-140: 0 results

Colorectal cancer prevention

endocuff: 4 results

endo-cuff: 0 results

ecvision: 0 results

ec-vision: 0 results

ec-assisted: 0 results

aec110: 0 results

aec120: 0 results

aec130: 0 results

aec140: 0 results

aec-110: 0 results

aec-120: 0 results

aec-130: 0 results

aec-140: 0 results

Practice management

endocuff: 1 result

endo-cuff: 0 results

ecvision: 0 results

ec-vision: 0 results

ec-assisted: 0 results

aec110: 0 results

aec120: 0 results

aec130: 0 results

aec140: 0 results

aec-110: 0 results

aec-120: 0 results

aec-130: 0 results

aec-140: 0 results

Submitted not presented

Biliary/Pancreas

Colon

Colorectal Cancer Prevention

Esophagus

Functional bowel disease

GI bleeding

Inflammatory bowel disease

Interventional endoscopy

Liver

Practice management

Small intestine

Stomach

endocuff: 0 results

endo-cuff: 0 results

ecvision: 0 results

ec-vision: 0 results

ec-assisted: 0 results

aec110: 0 results

aec120: 0 results

aec130: 0 results

aec140: 0 results

aec-110: 0 results

aec-120: 0 results

aec-130: 0 results

aec-140: 0 results

General endoscopy

endocuff: 1 result

endo-cuff: 0 results

ecvision: 0 results

ec-vision: 0 results

ec-assisted: 0 results

aec110: 0 results

aec120: 0 results

aec130: 0 results

aec140: 0 results

aec-110: 0 results

aec-120: 0 results

aec-130: 0 results

aec-140: 0 results

British Society of Gastroenterology Annual Meeting 2017

Interface / URL: https://www.bsg.org.uk/asset/EC5F4988-861F-4398-A1FD39F41240FF85/

Database coverage dates: n/a

Search date: 07/02/18

Retrieved records: 0

Search strategy:

Abstract PDF book for the 2017 Annual Meeting (https://www.bsg.org.uk/asset/EC5F4988-861F-4398-A1FD39F41240FF85/) was searched using the Ctrl F function. The following terms were searched on individually:

endocuff: 0 results

endo-cuff: 0 results

ecvision: 0 results

ec-vision: 0 results

ec-assisted: results

aec110: 0 results

aec120: 0 results

aec130: 0 results

aec140: 0 results

aec-110: 0 results

aec-120: 0 results

aec-130: 0 results

aec-140: 0 results

United European Gastroenterology Week 2017

Interface / URL: https://www.ueg.eu/week/

Database coverage dates: n/a

Search date: 07/02/18

Retrieved records: 2

Search strategy:

The UEG library was searched at: https://www.ueg.eu/education/library/

Results were filtered by conference: 25th UEG Week 2017

The following terms were searched individually:

endocuff: 1 result

"endo-cuff": 0 results retrieved (1 result returned, but duplicate of above)

ecvision: 0 results

"ec-vision": 1 result

"ec-assisted": 0 results

"aec110": 0 results

"aec120": 0 results

"aec130": 0 results

"aec140": 0 results

"aec-110": 0 results

"aec-120": 0 results

"aec-130": 0 results

"aec-140": 0 results

10.1.5 Details of any additional searches, such as searches of company or professional organisation databases (include a description of each database).

All searches are described above.

10.1.6 The inclusion and exclusion criteria.

POPULATION

Studies of adult (over 18 years of age) patients scheduled for colon screening, colonic surveillance or diagnostic colonoscopy, due to any cause, were eligible for inclusion in this review. Where possible, extracted data separately for screening, surveillance and diagnostic procedures.

INTERVENTION

Studies that evaluate ENDOCUFF VISION® –assisted colonoscopies were eligible for inclusion in this review.

COMPARATORS

Studies that compare ENDOCUFF VISION®–assisted colonoscopies with standard colonoscopies (i.e. colonoscopies with no distal device attached) were eligible for inclusion in this review.

OUTCOMES

Clinical effects and safety outcomes

Studies were eligible for inclusion in the review if they reported data on one or more of the following clinical or safety outcomes:

- Detection rate:
    - Benign polyps (types, location)
    - Adenoma (types, location, definition used at each stage)
    - Cancers
- Device insertion and withdrawal time
- Duration of colonoscopy
- Caecal intubation rate

- Mean number of adenomas per patient (MAP)
- Miss rate (where recorded)
- Outcomes relating to patients' comfort and satisfaction
- Complications, including:
    - Removal of device due to patient issues
    - Device retrieval if detached from scope
- Adverse events, including:
    - Bowel perforation
    - Mucosal petechiae / scratches
    - Anal discomfort
- Long term outcomes
    - Incidence of subsequent interval cancers
    - Referral rates for specialist treatment and rates of subsequent surgery, chemotherapy and radiotherapy
    - Tumour recurrence after colonoscopic resection
    - Rate of repeat colonoscopy after electrocoagulation for angiodysplasia.

STUDY DESIGN

Randomised controlled trials (RCTs) of any size and duration will be considered for inclusion in the clinical effects and safety review.

Non-randomised comparative and uncontrolled studies will be eligible for inclusion if they report relevant clinical effectiveness or safety data for

ENDOCUFF™ or ENDOCUFF VISION®. Non comparative or single arm studies will be eligible if they provide relevant safety data.

Studies published as abstracts or conference presentations only, and data from unpublished RCTs will be eligible for inclusion in the review if adequate data are provided. Systematic reviews will be identified and assessed as a source of references to primary studies.

LIMITS

No language limits will be applied to the searches. A date limit of 2010 to the current period will be applied; this is the earliest possible date the research team believes studies of ENDOCUFF™ could have been published. Studies reported in languages other than English will not be extracted, but will be listed for information only.

10.1.7 The data abstraction strategy.

One reviewer extracted data from each of the eligible studies, with a second reviewer checking each data point of the extracted data. Any discrepancies were resolved through discussion or by consulting a third reviewer.

Clinical effects and safety review

For trials that evaluate clinical efficacy and safety, we extracted the following information where reported:

- Trial details (bibliographic details)
- Trial characteristics:
    - Study design
    - Study objective
    - Details of randomisation and blinding
    - Number of participating centres and countries

    - Inclusion/exclusion criteria
    - Number of patients randomised/analysed
    - Follow up duration
    - Primary and secondary outcomes
- Patient baseline characteristics:
    - Age
    - Gender
    - Indication for colonoscopy
    - Any other disease specific characteristics of interest
- Details of procedure
- Person performing the endoscopy (incl. setting / type of unit):
    - Level of experience (e.g. number performed)
    - Quality of bowel preparation
    - Use of drugs during procedure (e.g. buscopan)
    - Requirements to move / manoeuvre patients
- Details of statistical analyses and how missing data were handled
- For each of the outcomes specified we will extract the following:
    - Outcome definition
    - The unit of measurement
    - The number of patients included in the analysis
    - The size of the effect:

        - For dichotomous outcomes; absolute and relative risks (or odds ratios) and risk (or rate) differences
        - For continuous outcomes; the mean change and measure of variance from baseline (or at both baseline and final visit), or mean difference between treatments
        - For time-to-event analysis; the number of events in each arm, median time to event and a hazard ratio and p-value
        - Where possible, absolute and relative data will be extracted
    - A measure of precision for each estimate of effect (95% confidence intervals, standard error or standard deviation)
- Discussion and justification of definitions of any clinically important differences
- Reports of any other analyses performed, including subgroup analysis and adjusted analyses, indicating whether they are pre-specified or exploratory

10.2 Appendix 2: Search Strategy for Adverse Events (Section 7.7.1)

The following information should be provided.

10.2.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

See Section 10.1.1.

10.2.2 The date on which the search was conducted.

See Section 10.1.2.

10.2.3 The date span of the search.

See Section 10.1.3.

10.2.4 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).

See Section 10.1.4.

10.2.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

See Section 10.1.5.

10.2.6 The inclusion and exclusion criteria.

See Section 10.1.6.

10.2.7 The data abstraction strategy.

See Section 10.1.7.

10.3 Appendix 3: Search Strategy for Economic Evidence (Section 8.1.1)

The following information should be provided.

10.3.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- EconLIT
- NHS EED.

See Section 10.1.1.

10.3.2 The date on which the search was conducted.

See Section 10.1.2.

10.3.3 The date span of the search.

See Section 10.1.3.

10.3.4 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).

See Section 10.1.4.

10.3.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

See Section 10.1.5.

10.4 Appendix 4: Resource Identification, Measurement and Valuation (Section 9.3.2)

The following information should be provided.

10.4.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- NHS EED
- EconLIT.

Response

10.4.2 The date on which the search was conducted.

Response

10.4.3 The date span of the search.

Response

10.4.4 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).

Response

10.4.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Response

10.4.6 The inclusion and exclusion criteria.

Response

10.4.7 The data abstraction strategy.

Response

11 Related Procedures for Evidence Submission

11.1 Cost models

An electronic executable version of the cost model should be submitted to NICE with the full submission.

NICE accepts executable cost models using standard software – that is, Excel, TreeAge Pro, R or WinBUGs. If you plan to submit a model in a non-standard package, NICE should be informed in advance. NICE, in association with the External Assessment Centre, will investigate whether the requested software is acceptable, and establish if you need to provide NICE and the External Assessment Centre with temporary licences for the non-standard software for the duration of the assessment. NICE reserves the right to reject cost models in non-standard software. A fully executable electronic copy of the model must be submitted to NICE with full access to the programming code. Care should be taken to ensure that the submitted versions of the model programme and the written content of the evidence submission match.

NICE may distribute the executable version of the cost model to a consultee if they request it. If a request is received, NICE will release the model as long as it does not contain information that was designated confidential by the model owner, or the confidential material can be redacted by the model owner without producing severe limitations on the functionality of the model. The consultee will be advised that the model is protected by intellectual property rights, and can be used only for the purposes of commenting on the model's reliability and informing comments on the medical technology consultation document.

Sponsors must ensure that all relevant material pertinent to the decision problem has been disclosed to NICE at the time of submission. NICE may request additional information not submitted in the original submission of evidence. Any other information will be accepted at NICE's discretion.

When making a full submission, sponsors should check that:

- An electronic copy of the submission has been given to NICE with all confidential information highlighted and underlined
- A copy of the instructions for use, regulatory documentation and quality systems certificate have been submitted
- An executable electronic copy of the cost model has been submitted
- The checklist of confidential information provided by NICE has been completed and submitted
- A PDF version of all studies (or other appropriate format for unpublished data, for example, a structured abstract) included in the submission have been submitted

11.2 Disclosure of Information

To ensure that the assessment process is as transparent as possible, NICE considers it highly desirable that evidence pivotal to the Medical Technologies Advisory Committee's decisions should be publicly available at the point of issuing the medical technology consultation document and medical technology guidance.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence').

When data are 'commercial in confidence' or 'academic in confidence', it is the sponsor's responsibility to highlight such data clearly, and to provide reasons why they are confidential and the timescale within which they will remain confidential. The checklist of confidential information should be completed: if it is not provided, NICE will assume that there is no confidential information in the submission. It is the responsibility of the manufacturer or sponsor to ensure that the confidential information checklist is kept up to date.

It is the responsibility of the sponsor to ensure that any confidential information in their evidence submission is clearly underlined and highlighted correctly. NICE is assured that information marked ‘academic in confidence’ can be presented and discussed during the public part of the Medical Technologies Advisory Committee meeting. NICE is confident that such public presentation does not affect the subsequent publication of the information, which is the prerequisite allowing for the marking of information as ‘academic in confidence’.

Please therefore underline all confidential information, and highlight information that is submitted under ‘commercial in confidence’ in blue and information submitted under ‘academic in confidence’ in yellow.

NICE will ask sponsors to reconsider restrictions on the release of data if there appears to be no obvious reason for the restrictions, or if such restrictions would make it difficult or impossible for NICE to show the evidential basis for its guidance. Information that has been put into the public domain, anywhere in the world, cannot be marked as confidential.

Confidential information submitted will be made available for review by the External Assessment Centre and the Medical Technologies Advisory Committee. NICE will at all times seek to protect the confidentiality of the information submitted, but nothing will restrict the disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

The Freedom of Information Act 2000, which came into force on 1 January 2005, enables any person to obtain information from public authorities such as NICE. The Act obliges NICE to respond to requests about the recorded information it holds, and it gives people a right of access to that information. This obligation extends to submissions made to NICE. Information that is designated as ‘commercial in confidence’ may be exempt under the Act. On receipt of a request for information, the NICE secretariat will make every effort to contact the designated company representative to confirm the status of any

information previously deemed ‘commercial in confidence’ before making any decision on disclosure.

11.3 Equality

NICE is committed to promoting equality and eliminating unlawful discrimination, including paying particular attention to groups protected by equalities legislation. The scoping process is designed to identify groups who are relevant to the evaluation of the technology, and to reflect the diversity of the population. NICE consults on whether there are any issues relevant to equalities within the scope of the evaluation, or if there is information that could be included in the evidence presented to the Medical Technologies Advisory Committee to enable them to take account of equalities issues when developing guidance.

Evidence submitters are asked to consider whether the chosen decision problem could be impacted by NICE’s responsibility in this respect, including when considering subgroups and access to recommendations that use a clinical or biological criterion.

For further information, please see the NICE website (www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp).

NICE National Institute for Health and Care Excellence

Expert adviser collated comments table

MT250 Endocuff Vision for endoscopic investigation

EAC questions for experts

The EAC contacted the below expert advisers with questions on the technology when beginning work on the assessment report. Below are the questions sent and responses received.

Expert #1	Dr Neil Cripps, Consultant Colorectal Surgeon and Chair, Colonoscopy Sub-Committee ACPGBI, Western Sussex Hospitals
Expert #2	Dr Anjan Dhar, Consultant Gastroenterologist, Clinical Lead for Gastroenterology and UGI Cancers, County Durham & Darlington NHS Foundation Trust
Expert #3	Dr Noriko Suzuki, Consultant Endoscopist, St Marks' Hospital, London North West University Healthcare NHS Trust

#	Question	Expert responses	
1	The sponsor in their submission did not consider the results of the E-Cap study because they claim that the baseline adenoma detection rate (ADR) of 58.9 % in the FOBT-positive screening population before the start of the study, was a lot	Expert #1:	Yes. This is agreed. The ADR in this group is already higher than the average even in a FOBT +ve population and certainly higher than a non FOBT +ve population. There is no study (that I am aware of) that gives us an accurate adenoma prevalence in any age group though that will vary with age and diet.
		Expert #2:	Yes.

	higher than the national average ADR (Logan et al. 2012). They claim that the reported ADR from the E-CAP study are considerably higher than the minimal standard (15%) and aspirational target (20%) for ADR set by the British Society for Gastroenterology. Do you agree with this statement?	Expert #3:	I think that "ADR set by BSG" is for symptomatic patients. Minimal standard of ADR for Colon cancer screening population is >40%, set by JAG. From the viewpoint, ADR of 58.9% is higher enough. The result of E-cap study should be considered.
2	Following to the previous question, is it likely that the increase in ADR seen with Endocuff Vision could be different between experienced and less experienced endoscopists, with the former group not showing much benefit because their baseline ADR is already high?	Expert #1:	I think this statement is correct. One group in Portsmouth Bowel Cancer Screening found no difference between Endocuff and not in a screening population. I have not noticed a difference personally in a limited number of patients. Indeed, in some instances the presence of Endocuff may impede adenoma removal.
		Expert #2:	Possibly, although the effect is likely to be a combination of the patient cohort (this study was done only in the BCSP population, which is a polyp enriched population, as contrasted from a symptomatic population, a polyp non enriched cohort) and the experience of the colonoscopist (highly experienced colonoscopists in the BCSP).
		Expert #3:	I agree with this. I assume that less experienced endoscopists group would have most benefit of using Endocuff. This is the reason of the difference in result between E-cap study and ADENOMA study.
3	The ADR is considered a key performance indicator and quality assurance standard for colonoscopy. Is there robust evidence	Expert #1:	There is direct evidence (NEJM) that the higher the ADR, the lower the interval cancer rate. Something like a 1% reduction of interval cancer for every 3% increase in ADR

	that a high ADR results in better clinical outcomes for the population?	Expert #2:	Yes, for prevention of colorectal cancer.
		Expert #3:	The key paper (Adenoma Detection Rate and Risk of Colorectal Cancer and Death NEJM 2014 April) suggested adenoma detection rate was inversely associated with the risks of interval colorectal cancer, advanced-stage interval cancer, and fatal interval cancer.
4	With the exception of the adenoma detection rate (ADR), are you aware of any other high quality evidence (RCT) that support the relationship between another index such as for example PDR and a reduction in interval cancers?	Expert #1:	We use PDR as a surrogate marker for ADR but I am not aware of any RCT evidence for it or any other KPI that shows such reduction.
		Expert #2:	No, ADR remains the best metric for reduction of interval cancers, and PDR is a less accurate and crude matric for the same. PDR relates to polyp detection rate (where the nature of the polyp has not been confirmed to be an adenoma, and so is less accurate since hyperplastic polyps, which do not have any relationship to colorectal cancers may also be included in PDR
		Expert #3:	No.
5	The ADENOMA RCT (Ngu 2018) included patients >18 years old, is ADR applicable to any population or the formal definition requires a population > 50 years old? How can the inclusion of a lower age group may have influenced the results?	Expert #1:	Adenoma peak prevalence is in the late 50s and they are more common in males. Inclusion of a young, more female population would influence the numbers of adenomas available for detection.
		Expert #2:	ADR is usually applicable to the screening population only since the aim of preventing colorectal cancer relates to this population. Since not many younger patients than 50years old have screening colonoscopy the concept of ADR influencing CRC rates and reducing the incidence of colon cancer can only be

			applied to the screening population over the age 50 in an epidemiological concept. Reducing adenomas in a younger population or cohort of symptomatic patients will also reduce CRC incidence but not in an epidemiological context.
		Expert #3:	ADR is applicable for any population. This study included lower age group and also "symptomatic" patients. These may contribute to lower adenoma detection rate. We need to clarify ADR for symptomatic patients or for the screening population.
6	Is there a difference in the ADR between men and women (higher for men) and would you expect a study with a higher proportion of men to result in higher ADR for the intervention and the comparator cohort?	Expert #1:	Yes, as above
		Expert #2:	Yes, ADRs are usually higher in men since more polyps are found in men in a screening population. So the impact of ADR on CRC is higher for men.
		Expert #3:	Gender would be the one of the factor and there is a possibility to affect the result of ADR
7	Is this paper Lee et al 2012 the best and most recent evidence on the quality of colonoscopy in the UK? Are you aware of a most recent national audit?	Expert #1:	I don't know of a more recent national audit. The National Endoscopy database is starting up but there is no form outturn yet.
		Expert #2:	No. The best audit on colonoscopy is produced annually from the BSCP. See also Gavin DR, et al. Gut 2013;62(2):249.
		Expert #3:	No.

8	What would be the best source to retrieve relevant colonoscopists' experience (highly experienced versus not so) in the UK?	Expert #1:	I don't know. The Ned will allow comparison between data in those who do a lot of endoscopy, against those that don't. I don't know how ready the database is for data extraction yet.
		Expert #2:	The national endoscopy database (NED).
		Expert #3:	To check if JAG accredited colonoscopists or not.
9	What proportion of colonoscopies would require a repeat colonoscopy? Is the main reason for repeat colonoscopy inadequate bowel preparation? The national audit listed above reports that *'The mean proportion of procedures in which the bowel preparation was excellent or adequate was 94.2% (range 81.5-100%).'* Is this number representative of the practice nationally?	Expert #1:	About 30% of colonoscopy is repeated for adenoma follow up but this is a poor indication because guidelines are over protective. Lots of colonoscopy is impaired by lack of adequate preparation, perhaps 25%, but we don't routinely repeat for that unless it is appallingly bad, largely because we haven't got the capacity and those that prep poorly are largely going to prep poorly next time too. It is a question of compliance.
		Expert #2:	Yes. Less than 5% repeat colonoscopies, most commonly for poor bowel prep or for poor patient tolerance.
		Expert #3:	The inadequate bowel prep is indeed the common reason for a repeat procedure. "Around 5% of the patient presented poor prep nationally" sounds very fair.

10	The E-Cap RCT reported unusually high caecal intubation and withdrawal times (approximately 16min and 17-19min, respectively please see attached document). The sponsor claims that this difference was driven by a difference in the definition of withdrawal time in the E-CAP study compared to the other three included studies. Is this the case? Is there an official definition of withdrawal time for colonoscopy?  Bhattacharyya Endoscopy 2017.pdf	Expert #1:	The intubation times are quite long but comparable between groups. The extubation times are indeed statistically different but not clinically so; the saving of 12 or so minutes/list assuming 4 cases is of no importance. The ADR rates are the key. There is a minimum standard for colonoscopy of some 6 minutes (in BCS cases) with an aspiration for 10 minutes. It is important to recognise that these values are generally measured in people in whom no polyps are found. Longer withdrawal times may reflect the time taken for endotherapy but I can't confirm this. Maybe you'd look too? There will be an observer tendency in the trial set up to look harder for polyps than a) in the general population and b) in Screening patients but the ADR is similar in my own unit. I would agree that there seems no benefit in routine use of EndoCuff on this evidence.
		Expert #2:	I am not clear about the interpretation of the sponsor – [it would be good to] clarify as to what they mean by "a difference in the definition of Withdrawal time in the E-cap study compared to the other three studies"? The standard accepted definition as per the UK National Bowel Cancer Screening Programme Quality Assurance Manual is the mean time taken to withdraw the colonoscope from the caecal pole to the anus. (NHS BCSP Publication No. 6, February 2011). This document is available on the NHS Cancer Screening Programmes website.
		Expert #3:	N/A

11	Do you use pre-test probabilities to define the adenoma detection rates for different populations (screening vs. symptomatic populations)? If yes, are you aware of any resources that may provide this information?	Expert #1:	We don't particularly prospectively do that but: 1. The data in screening is much better in that histology is known of all polyps so that an ADR can be defined definitively. The minimum standard is 40% 2. In symptomatic disease, there is an indicative Polyp (not adenoma) detection rate of 25% - much lower than screening because there are younger patients who are being investigated for different reasons. There is also a different standard for men (higher) and women (lower). This information should be available in the BCS Standards and JAG standards for colonoscopy.
		Expert #2:	The predefined ADR for the screening population is 25% but for symptomatic population is 15%.
		Expert #3:	From the pilot study and previous experiences, we have got a standard target of adenoma detection rate in bowel cancer screening. But it would be extremely difficult to set up the targeted adenoma detection rate. I will check if JAG (joint advisory group) set the standard for adenoma detection rate for symptomatic population).

NICE briefing note expert questionnaire

NICE contacted a number of experts during the production of a briefing note on the Endocuff technology in 2014. Guidance development began in 2018 following the publication of the ADENOMA trial, at which point NICE contacted the below experts to confirm their responses were still current and giving them the opportunity to update them in light of further experience. 2 further experts were added (Dr Cripps and Dr Ayaru) who were asked to complete the same questionnaire. The questions sent and responses received are included below.

Name of Expert Advisers	Job Title
Professor Colin Rees	**Consultant Gastroenterologist + Professor of GI Endoscopy**
Dr Anjan Dhar	**Reader in Medicine (Durham), Consultant Gastroenterologist and Clinical Lead for Gastroenterology, County Durham**
Dr Neil Cripps	**Consultant Colorectal Surgeon, Western Sussex Hospitals NHS Foundation Trust**
Dr Noriko Suzuki	**Honorary Consultant Endoscopist, St Mark's Hospital**
Dr Lakshmana Ayaru	**Consultant Gastroenterologist, Imperial College Healthcare NHS Trust**

YOUR PERSONAL EXPERIENCE (IF ANY) WITH THIS TECHNOLOGY

Question 2: Please indicate your experience with this technology?

Expert Advisers	I have had direct involvement with this	I have referred patients for its use	I manage patients on whom it is used in another part of their care pathway	I would like to use this technology but it is not currently available to me
Professor Colin Rees	**Yes**	Blank	Blank	Blank
Dr Anjan Dhar	**Yes**	Blank	**Yes**	Blank
Dr Neil Cripps	**Yes**	**No**	**No**	**No**
Dr Noriko Suzuki	**Yes**	Blank	Blank	Blank
Dr Lakshmana Ayaru	**Yes**	**No**	**No**	**No**
Any Comments?				
None				

Question 3: Have you been involved in any kind of research on this technology? If Yes, please describe?

Expert Advisers	Yes/No	Comment
Professor Colin Rees	**Yes**	**I am CI on a multi centre RCT of this device - starting November 2014**
Dr Anjan Dhar	**Yes**	**I was a member of the Data Monitoring Committee for a clinical trial that used this product (ADENOMA Trial) and have reviewed the data collected for the trial and the publication of the paper**
Dr Neil Cripps	**No**	
Dr Noriko Suzuki	**Yes**	Tsiamoulos ZP et al. Impact of a new distal attachment on colonoscopy performance in an academic screening center. Gastrointest Endosc. 2018 Jan;87(1):280-287
Dr Lakshmana Ayaru	**No**	

THIS PRODUCT (TECHNOLOGY) AND ITS USE

Question 4: How would you best describe this technology?

Expert Advisers	It is a minor variation on existing technologies with little potential for different outcomes and impact	It is a significant modification of an existing technology with real potential for different outcomes and impact	It is thoroughly novel - different in concept and/ or design to any existing
Professor Colin Rees	Blank	**Yes**	Blank
Dr Anjan Dhar	Blank	Blank	**Yes**
Dr Neil Cripps	**Yes**	Blank	Blank
Dr Noriko Suzuki	**Yes**	Blank	Blank
Dr Lakshmana Ayaru	Blank	**Yes**	Blank
Any Comments?			
Dr Anjan Dhar	**This technology is based on the concept of improving visualisation of the entire colon to detect polyps and adenomas by opening out the folds in the colon. It is effective in its ability to do that but needs to be used in the right patient, ideally in the screening and surveillance population and not for all colonoscopies carried out for any other indication.**		

Question 5: What is the most appropriate use (e.g. clinical indication) for the technology?

Expert Advisers	Comment
Professor Colin Rees	**Routine NHS colonoscopy**
Dr Anjan Dhar	**This technology is ideally recommended for use in the bowel cancer screening population and in the surveillance of patients with previously found polyps (both BCSP and symptomatic populations). It should not be recommended for all colonoscopies in the symptomatic population, especially in patients with diarrhoea and inflammatory bowel disease.**
Dr Neil Cripps	**For use during colonoscopy to attempt to improve adenoma detection rates.**
Dr Noriko Suzuki	**This technology would be used to enhance lesion detection in the patient with previous history of colorectal polyp in the bowel cancer screening.** **From my own personal experience, this cuff facilitate the insertion of colonoscopy in patients with long and loopy colon.**
Dr Lakshmana Ayaru	**1.To enhance polyp detection rate during colonoscopy** **2. To aid resection of polyps wrapped behind colonic folds**

COMPARATORS (including both products in current routine use and also "competing products")

Question 6: Given what you stated is the appropriate indication (clinical scenario) for its use, what are the most appropriate "comparators" for this technology which are in routine current use in the NHS?

Expert Advisers	Comment
Professor Colin Rees	Non cuff assisted colonoscopy - comparison of adenoma detection rate
Dr Anjan Dhar	None
Dr Neil Cripps	Transparent colonoscopy caps
Dr Noriko Suzuki	For the lesion detection, Olympus distal attachment.
Dr Lakshmana Ayaru	1. Compare with standard HD colonoscopy, transparent caps

Question 7: "Competing products": Are you aware of any other products which have been introduced with the same purpose as this one?

Expert Advisers	Comment
Professor Colin Rees	Endoscopic cap
Dr Anjan Dhar	Yes, Endo-ring and standard clear cap
Dr Neil Cripps	Similar devices from other manufacturers
Dr Noriko Suzuki	Endorings has the same concept of Endocuff, which was developed after endocuff.
Dr Lakshmana Ayaru	Endorings

POSSIBLE BENEFITS FOR PATIENTS

Question 8: What are the likely additional benefits for patients of using this technology, compared with current practice/ comparators?

Expert Advisers	Comment
Professor Colin Rees	Improved ADR and reduced miss rates of adenomas
Dr Anjan Dhar	Improved detection of colonic polyps (adenomas, precursors of colon cancer) and their removal leading to a decrease in colon cancer rates.
Dr Neil Cripps	Improved adenoma detection rates. Reduced interval cancer incidence.
Dr Noriko Suzuki	Adenoma miss rate would be reduced leading to the decrease in interval cancer.
Dr Lakshmana Ayaru	Increased adenoma detection rate in a screened population which may reduce the risk of developing interval colorectal cancer (although later is not proven)

Question 8.1: Is each additional benefit likely to be realised in practice? What are the likely obstacles?

Expert Advisers	Comment
Professor Colin Rees	Yes
Dr Anjan Dhar	Longer procedure time leading to a lower number of patients being scoped on a list.
Dr Neil Cripps	There are conflicting reports of benefit in increased ADR The Post Colonoscopy Colorectal Cancer Rate would take a number of years to alter and there would have to a large RCT to show this. There is no current study demonstrating this.
Dr Noriko Suzuki	Adenoma detection rate would be increased. Likely obstacles would be the cost of Endocuff. The majority of additional lesions detected with this technology would be small benign lesions which will not have clinical importance.

Expert Advisers	Comment
Dr Lakshmana Ayaru	The additional adenoma detection seems to be best realised in FOBT positive cases rather than for routine symptomatic colonoscopy The benefit may be best realised if used by endoscopists with low to moderate adenoma detection rates Some data that completion of colonoscopy may be slightly lower with use of endocuffs due to diverticular disease and anal pain on insertion. However other studies do not show a lower completion rate with endocuff use.

Question 8.2: How might these benefits be measured? What specific outcome measures would enable assessment of whether additional benefits for patients are being realised?

Expert Advisers	Comment
Professor Colin Rees	RCT such as the one I am about to commence
Dr Anjan Dhar	Adenoma detection rates (ADR), mean number of adenomas detected per patient
Dr Neil Cripps	As Above
Dr Noriko Suzuki	It would be measured by the increase in adenoma detection rate and decrease in interval cancer rate Long term observation is needed.
Dr Lakshmana Ayaru	Adenoma detection rate and mean adenoma per procedure

Question 8.3: How good is this evidence for each of these additional benefits?

Expert Advisers	Comment
Professor Colin Rees	RCT needed
Dr Anjan Dhar	Very good – ADR coorelates very well to decrease in colon cancer rates.
Dr Neil Cripps	Small studies have been undertaken. A large RCT would be necessary with a long follow up to show definite benefit.
Dr Noriko Suzuki	very reliable
Dr Lakshmana Ayaru	Low to Moderate quality evidence (based on which meta-analysis you read)

Question 8.4: Please add any further comment on the claimed benefits of the technology to patients, as you see applicable

Expert Advisers	Comment
Professor Colin Rees	I believe this technology to be potentially hugely beneficial but trial eveidence is required
Dr Anjan Dhar	Blank
Dr Neil Cripps	Blank
Dr Noriko Suzuki	Blank
Dr Lakshmana Ayaru	Blank

POSSIBLE BENEFITS FOR THE HEALTHCARE SYSTEM

Question 9: What are the likely additional benefits for the healthcare system of using this technology, compared with current practice/ comparators?

Expert Advisers	Comment
Professor Colin Rees	**Reduce colorectal cancer rates**
Dr Anjan Dhar	**Decrease in colon cancer rates nationally reducing the cost of care for colorectal cancers**
Dr Neil Cripps	**Reduced bowel cancer incidence**
Dr Noriko Suzuki	**Blank**
Dr Lakshmana Ayaru	**Blank**

Question 9.1: Is each additional benefit likely to be realised in practice? What are the likely obstacles?

Expert Advisers	Comment
Professor Colin Rees	**Yes. Obstacles are belief in evidence and small cost**
Dr Anjan Dhar	**Yes**
Dr Neil Cripps	**Long follow up would be needed in an RCT**
Dr Noriko Suzuki	**The decrease in interval cancer rate could be observed in long term.**
Dr Lakshmana Ayaru	**Increased adenoma detection rate in a screened population which may reduce the risk of developing interval colorectal cancer (although later is not proven)**

Question 9.2: How might these benefits be measured? What specific outcome measures would enable assessment of whether additional benefits for the healthcare system are being realised?

Expert Advisers	Comment
Professor Colin Rees	RCT
Dr Anjan Dhar	National database for colorectal cancers will be able to show benefits for each local region after implementation of this device in colonoscopy practice in the region
Dr Neil Cripps	Blank
Dr Noriko Suzuki	Need to use bowel cancer screening national database
Dr Lakshmana Ayaru	The additional adenoma detection seems to be best realised in FOBT positive cases rather than for routine symptomatic colonoscopy The benefit may best realised if used by endoscopists with low to moderate adenoma detection rates

Question 9.3: How good is this evidence for each of these additional benefits?

Expert Advisers	Comment
Professor Colin Rees	RCT required
Dr Anjan Dhar	Blank
Dr Neil Cripps	Blank
Dr Noriko Suzuki	Very reliable but it would be substantially long term analysis.
Dr Lakshmana Ayaru	Blank

Question 9.4: Please add any further comment on the claimed benefits of the technology to the healthcare system, as you see applicable

Expert Advisers	Comment
Professor Colin Rees	**As above trial is needed**
Dr Anjan Dhar	**Blank**
Dr Neil Cripps	**Blank**
Dr Noriko Suzuki	**Blank**
Dr Lakshmana Ayaru	**Blank**

FACILITIES, TRAINING AND FUNCTIONING

Question 10: Are there any particular facilities or infrastructure which needs to be in place for the safe and effective use of this technology?

Expert Advisers	Comment
Professor Colin Rees	**Training**
Dr Anjan Dhar	**Training colonoscopists to use this safely, without any detachment.**
Dr Neil Cripps	**No**
Dr Noriko Suzuki	**No**
Dr Lakshmana Ayaru	**No**

Question 11: Is special training required to use this technology safely and effectively?

Expert Advisers	Comment
Professor Colin Rees	Yes
Dr Anjan Dhar	Yes
Dr Neil Cripps	No
Dr Noriko Suzuki	This technology is easy to apply to daily practice. No special training is required.
Dr Lakshmana Ayaru	No

Question 12: Please comment on any issues relating to the functioning, reliability and maintenance of this technology which may be important to consider if it is introduced

Expert Advisers	Comment
Professor Colin Rees	potential for some increased anal discomfort should be measured
Dr Anjan Dhar	Good technology with a good safety record and no significant adverse events reported in the trial and post marketing surveillance
Dr Neil Cripps	A new Endocuff would be necessary for each case.
Dr Noriko Suzuki	There are some cases where endocuff is not functioning, especially in severe diverticular disease, endocuff should be taken off.
Dr Lakshmana Ayaru	Blank

COSTS

Question 13: Please provide any comments on the likely cost consequences of introducing this technology. In particular, please comment on the implications of this technology replacing the comparator/s you have described above

Expert Advisers	Comment
Professor Colin Rees	Small given overall gain
Dr Anjan Dhar	Additional direct cost of the device, and possibly some indirect costs of reduction in capacity
Dr Neil Cripps	Circa £12/colonoscopy
Dr Noriko Suzuki	The time horizon for the cost analysis will be sufficiently long to reflect any differences in costs and consequences between the technologies being compared. There is comparator "Endorings".
Dr Lakshmana Ayaru	Costs approx. £12 for one cuff (box of 8 =£96.40)

GENERAL ADVICE BASED ON YOUR SPECIALIST KNOWLEDGE

Question 14: Is there controversy about any aspect of this technology or about the care pathway?

Expert Advisers	Comment
Professor Colin Rees	The evidence is not complete as there are no large trials
Dr Anjan Dhar	Yes. There is a general drive to use this technology for all colonoscopies which is not evidence based or appropriate to its results in the trial
Dr Neil Cripps	No
Dr Noriko Suzuki	There has been no data comparing Endocuff and comparators in adenoma detection rate.
Dr Lakshmana Ayaru	It is unclear as to whether this technology will lead to increased adenoma detection rates in colonoscopist who have high ADR(variable definitions of this (conflicting evidence)

Question 15: If NICE were to develop guidance on this technology, how useful would this be to you and your colleagues?

Expert Advisers	Comment
Professor Colin Rees	Hugely (if evidence proves it's value)
Dr Anjan Dhar	Moderately useful
Dr Neil Cripps	Useful
Dr Noriko Suzuki	It would encourage the regular supply of Endocuff via NHS.
Dr Lakshmana Ayaru	Blank

Question 16: Do any subgroups of patients need special consideration in relation to the technology (for example, because they have higher levels of ill health, poorer outcomes, problems accessing or using treatments or procedures)? Please explain why

Expert Advisers	Comment
Professor Colin Rees	potential significant benefot for bowel cancer screening patients,
Dr Anjan Dhar	Patients with suspected or proven inflammatory bowel disease are contraindicated for the use of this device.
Dr Neil Cripps	No
Dr Noriko Suzuki	For the patients with severe diverticular disease or fixed colon, the use of endocuff would disturb colonoscopy insertion.
Dr Lakshmana Ayaru	Blank

CONFLICTS OF INTEREST

Question 18.1: ***Do you or a member of your family have a personal pecuniary interest? The main examples are as follows:***

Expert Advisers	Consultancies or directorships	Fee-paid work	Shareholdings	Expenses and hospitality	Investments	Personal non-pecuniary interest
Professor Colin Rees	**Yes**	No	No	Blank	No	**Yes**
Dr Anjan Dhar	**Yes**	Blank	Blank	Blank	Blank	Blank
Dr Neil Cripps	**No**	**No**	**No**	**No**	**No**	**No**
Dr Noriko Suzuki	**No**	**No**	**No**	**No**	**No**	**No**

If you have answered YES to any of the above statements please describe the nature of the conflict(s) below.

Professor Colin Rees	It does not fall under any of above but as stated I am about to lead an NIHR adopted industry funded (ARC medical £130 000) trial of this device
Dr Anjan Dhar	*Member of the Data Monitoring Committee for the ADENOMA Clinical Trial* I was a member of the Data Monitoring Committee for the ADENOMA Clinical trial which evaluated the role of Endocuff Vision, and I do not think that this role conflicts with my ability to comment on the NICE Guidance Development Programme.

Question 18.2: Do you have a non-personal interest? The main examples are as follows:

Expert Advisers	Fellowships endowed by the healthcare industry	Support by the healthcare industry or NICE that benefits his/her position or department, e.g. grants, sponsorship of posts
Professor Colin Rees	No	No
Dr Anjan Dhar	Blank	Blank
Dr Neil Cripps	No	No
Dr Noriko Suzuki	No	No

NICE National Institute for Health and Care Excellence

Expert adviser collated comments table

MT250 Endocuff

Expertise advice was sought from Dr Geoff Smith, a member of the clinical team at the Joint Advisory Group (JAG) on gastrointestinal endoscopy, concerning the JAG accreditation process in general, the available evidence for Endocuff Vision and other key considerations around the use of the technology.

Expert	Dr Geoff Smith, Chair of the Quality Assurance of Training Working Group (QATWG) at the JAG, luminal gastroenterologist at Imperial College Healthcare NHS Trust, London, and Chair of the Bowel Cancer Screening MCQ group.

#	Topic	Expert response
1	Overview of JAG accreditation process	• The general certification for colonoscopists has been managed by JAG for 12-13 years. It is the first certification of its kind internationally and the only certification for endoscopy in the UK • To gain accreditation, individuals will require a minimum target of 200 completed procedures and demonstrate that they can perform the procedure to JAG standards. This will include procedures directly observed by a supervisor. For end-certification, individuals are required to perform 4 independent procedures to JAG standards • Individuals will also be evaluated on how well they remove polyps and will progress through grade difficulties – from easy to moderate and difficult removal of polyps • JAG accreditation is open to any healthcare professional who is registered with a regulatory body i.e. doctors or nurses. People typically enter the accreditation process via 3 main routes: o Doctor training – gastroenterologists and surgeons

		○ Other Healthcare Professionals – endoscopy nurses undertaking a degree based programme ○ National Health Education England clinical endoscopist programme – Upper GI and Flexible sigmoidoscopy • Certification may be provisional or final. People with provisional certification can still practice but may require some level of support • JAG accreditation is not nominally mandatory however, in an NHS setting, it is expected that endoscopists are JAG certified. There are established endoscopists i.e. those with ~20 years of experience that are not required to do the certification process now. • There is a separate accreditation required for a British Cancer Screening Programme (BCSP) endoscopist which is run by the screening programme. This involves an MCQ test to demonstrate sufficient knowledge as well as being observed doing the procedure by 2 external assessors • A centre may also be 'JAG certified' if they can provide clear evidence that their equipment and facilities are to JAG standards. It also involves KPI reporting on procedure access times. This is reviewed every 3-5 years. Most UK units have sought JAG accreditation but not all have been awarded. • ADR is a key performance indicator for individuals applying for JAG accreditation but not for centres

2	The use of ADR as a marker for colonoscopy quality	• ADR is a good surrogate marker of endoscopy quality however it is influenced by a number of factors: o How long the endoscopist spends inspecting the walls of the bowel – evidence shows that ADR increases with time from 0-11 minutes, and plateaus after that o Assessor fatigue i.e. ADR can be lower for procedures done at the end of a morning or afternoon list o Level of resolution and how well kit is working (extraneous cognitive load)
3	Colonoscopist 'experience' or 'expertise', and comments on the term 'expert'	• Agreed with the term 'expertise' over 'experience' • Screening colonoscopists could be regarded as 'experts' due to the selection/accreditation process o There is a ~25% variation in baseline ADRs between the top and bottom performing BCSP endoscopists • The separate accreditation process for screening endoscopists has created a 2-tiered system. From an education and training perspective, would like to move away from 'expert' and 'non-expert' – JAG expects the same quality standards to be met irrespective of training and educational background • 'Very high endoscopy standards', 'skill-based competence' or 'procedural-based capabilities' are what determines an expert colonoscopist
4	The differences between screening and non-screening populations	• Standard ADR levels are dependent on how a patient is referred o BCSP: achievable level of 40% ADR with a target level of 50% ADR o General population: 20-25% ADR • In unselected centres average baseline ADR may be 20-25%, but there is wide variation in that

		• For a centre with lower ADR, it can be hard to tell whether this is due to differences in patient population or in endoscopy quality • In a real-world setting, it is difficult to determine the correct average baseline ADR for the different populations of patients referred for endoscopy – the national endoscopy database may help uncover this information
5	Study design and quality of clinical evidence	• Studies could not be blinded and involved centres interested in the technology – ADR would have been influenced by how well the walls of the bowel were washed and how long the endoscopist spent checking for adenomas • ADENOMA trial design was OK but could have been more robust however the nature of Endocuff means blinding is not feasible • The ADR uplift is not as high in reality with ITT • Endoscopists in the trial may have been using a particular type of endoscope that may have had an impact on handling , impacting on ease of use and mucosal visualisation, whereas real work experience anecdotally suggests that some combinations of 'scope and device are more effective than others • Has concerns about the way the ADENOMA trial reported discomfort scores
6	ADR outcomes in ADENOMA trial vs. real-world experience	• *ADR improvement in non-BCSP cohort (0.4%):* not surprised by the low level of ADR improvement for the general population – no. of procedures per individual was smaller and patients in this cohort would have had lower baseline ADR to start with • *ADR improvement in BCSP cohort* (10.8%): found the screening data interesting – experience from JAG and London centres is that ADR improvement is not as great with Endocuff Vision in real-world practice

7	Comments on the benefits of Endocuff Vision being dependent on colonoscopists expertise	• ADR is defined as the proportion of patients in whom you find >=1 adenoma, there may be a tendency to reach this number and stop looking further • Endocuff Vision is likely to increase the number of adenomas detected from 0 to 1 and would help improve ADR for endoscopists at the bottom end of the ADR scale i.e. 25-26% baseline ADR • Endoscopists in the upper range may already be doing a lot of things to increase their ADR, but they may see a little improvement with Endocuff Vision • A similar effect has been seen in other studies e.g. a Canadian study looking at withdrawal times found that when this was set to a minimum of 10 minutes, the biggest improvements in ADR were found in the bottom quartile of endoscopists (baseline ADR <40%) • Overall, non-blinded studies with ADR as an outcome are impossible to control. Because the assessor may be expecting an increase in adenoma detection they may be looking harder
8	Comments on the overall quality of endoscopy (ADR) across NHS	• For screening: 70% of endoscopists are median-level performers with 15% performing either side of that o Data has come from colonoscopy audit from 7/8 years ago o Figures based on self-reporting – quality of data is limited • For non-screening distributions are similar: 50-60% middle range with 20% either side of that • National endoscopy database should help confirm variations in standards across England and Wales: o Automated reporting system to report all procedures o Approximately 30-35% are uploading and another 25% are testing the process o ½ million procedures recorded to date o In current iteration recording the use of adjuncts can be reported but it is not mandatory o Consultation now closed and second iteration is planned to be rolled out in 2020

9	Is there a place for Endocuff Vision in training and JAG accreditation process?	• The first part of training is focused on achieving a comfortable insertion – due to effects on handling, use of the technology can make this challenging for trainees and uncomfortable for patients • Would only introduce the technology to trainees who have performed a minimum of 100-150 procedures • Can't see it being used mandatory as part of training
10	Patient selection for Endocuff Vision	• Although Endocuff can be used with most endoscopes, it can make handling of certain models more difficult. This may have an impact on ADR, polyp removal, and may make the procedure less comfortable for patients • Would only advise the use of the technology with certain models of scope and in selected patients: o Men – wouldn't recommend in women due to anatomical differences and challenges with intubation o Patients over the age of 50 – patients under 50 will have an overall lower risk of cancer and tend to be easier endoscopies therefore the benefit of using Endocuff vision may be outweighed by the insertion discomfort caused by increased instrument diameter o Patients already on polyp surveillance o Patients who have had previous procedures

11	Other comparable technologies	• Aware of comparable technologies used in USA and other countries • Data for these other technologies are not as robust • Yet to use these comparable technologies, but anecdotal evidence suggests they are just as good as Endocuff Vision • A lot of the uptake for Endocuff Vision may have been company-driven o This is a fast-moving field and it is likely that manufacturers of endoscopes will improve designs to better suit the needs of endoscopists
12	General comments	• Not convinced by the value of Endocuff Vision as an adjunct • Would not recommend for routine use but in selected patients only. The decision on whether or not to use the technology should be made on a patient-by-patient basis • Individual endoscopists may decide to use the technology if it has been shown to work for them and it increases their baseline ADR • Would advocate that the use of the device in screening population is not mandatory – would expect push back from colonoscopists • The uptake of Endocuff Vision has been less than predicted despite the company supplying free devices to units for screening cases • Main challenge for endoscopists is capacity vs. demand (5-7% increase in numbers referred for colonoscopy each year), resulting in an increase in weekend and evening lists, increase in size of work force and challenging nursing staff levels

National Institute for Health and Care Excellence

External Assessment Centre correspondence

MT250 Endocuff Vision

The purpose of this table is to show where the External Assessment Centre relied in their assessment of the topic on information or evidence not included in the sponsors' original submission. This is normally where the External Assessment Centre:

a) become aware of additional relevant evidence not submitted by the sponsor
b) need to check "real world" assumptions with NICE's expert advisers, or
c) need to ask the sponsor for additional information or data not included in the original submission, or
d) need 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 made available to MTAC. The table is presented to MTAC in the Assessment Report Overview, and is made available at public consultation.

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*	Action / Impact / Other comments
Clinical section	**Initial questions sent to manufacturer 29.06.18** **1.** The company claims that the improved visibility increases sensitivity with “no reduction in specificity” – is this right? i.e. has this been tested? **2.** One of the claims is that EndoCuff can be fitted to any endoscope but the IFU says it can only be used with “compatible endoscopes” – what are the incompatible endoscopes?	**Responses received from manufacturer during the TC 02.07.18 (see appendix 1a)** **1.** The sponsor answered that there has been no investigation of specificity in any of the papers but the assumption is that there is no reduction in specificity that would have impact economic evaluation for Endocuff vision. **2.** NS answered that there are some devices that Endocuff will not be used with but they are completely different types of technology. Pentax, Olympus among others produce new scopes and Norgine tests them – there will always be scopes that are not included in the compatibility schedule that are accessible online. There is not a definitive list of scopes that Endocuff does not fit but there is an existing list of devices Endocuff is compatible with, which accounts for 99% on the market.	

Clinical evidence section	**E-mail sent to manufacturer 09.07.18** **1.** Can you please clarify the original CE mark date for Endocuff Vision? The submission mentions August 2016 but we note that some of the included evidence patients were recruited prior to that date. **2.** The original Endocuff had different devices available with varying sizes for different colonoscopes. Is this the case for Endocuff Vision as well? If not, how did you address this issue by producing a single technology for all colonoscopes? **3.** The ADENOMA RCT had a high rate of non-eligible patients excluded (close to 25%). Can you provide more details on the reasons behind the high rate of ineligibility for inclusion?	**Response from manufacturer 12.07.18 (see below and appendix 2a)** **1.** For clarity the original CE mark was given in September 2014, and this was renewed in August 2016. **2.** There are 4 different Endocuff Vision sizes to fit different types of scope. These are detailed in section A of our submission. We have also attached the current interim compatibility schedule for ECV. **3.** Norgine does not have access to the unpublished ADENOMA data and are currently limited to the information that is contained in the publication. The reasons given in the ADENOMA study for a patient being classified as non-eligible are: • Pre-endoscopy suspicion of large bowel obstruction • Known colon cancer or polyposis syndromes • Known colonic stricture • Known severe diverticular segment • Known active colitis • On anticoagulants which had not been stopped preprocedure (meaning polypectomy might not be undertaken) • If pregnant or attending for a therapeutic procedure or assessment of a known lesion	

	Email sent to manufacturer and YHEC – 12.07.18 **1.** We were hoping to receive the Endnote file containing the 103 full text publications that were excluded with reasons as listed in your PRISMA flowchart (Figure B1 of your submission). If an Endnote file is not available can you please provide the list of references and the associated pdfs?	**Response from YHEC – 13.07.18 (see appendix 2b)** **1.** Yes of course, please find the list attached. We had these listed in an additional appendix but perhaps that did not make it to you. Of the 103 excluded studies listed in the PRISMA, there were 94 excluded with reasons and an additional 9 ongoing trials with no results. I've just spoken with Norgine and we are working to gather the PDF's of these records which we hope to get to you next week. Please note that there are quite a few trial registry records in there that will not have a 'full text' paper but the link to the registry record is included the reference. **Response from manufacturer – 25.07.18 (see appendix 2c)** My apologies for the delay in responding to your request, we have had to acquire papers where possible as we do not have them all on file. Additionally our access permissions prohibit some of the papers from being shared and we have had to check permissions. I have attached the papers that we are able to share.	

a) Minutes of teleconference with sponsor 02.07.18:

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Appendix 2

a) Attachments received in e-mail from sponsor dated 12.07.18:

b) Attachments received in e-mail from YHEC dated 13.07.18:

c) Attachments received in e-mail from sponsor dated 25.07.18:

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National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

External Assessment Centre Report factual check

Endocuff Vision for Endoscopic Investigation

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 KiTEC EAC to ensure there are no factual inaccuracies contained within it. If you do identify any factual inaccuracies you must inform NICE by **17:00pm (BST), Wednesday 22 August 2018** 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.

Issue 1

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 19: The text states "Patients were randomised 1:1 and were seen at 7 hospitals in the north east of England." This is incorrect.	Six of the seven hospitals were in the North East of England. The seventh was in London. The report text should be amended.	The information currently listed is incorrect. The correct information is detailed on clinicaltrials.gov (https://clinicaltrials.gov/ct2/show/NCT02552017?term=NCT+02552017&rank=1)	Thank you for the clarification we have amended the report accordingly.

Issue 2

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 23; The text states that table 4 and table 5 report 'patient and wound characteristics'	As no data on wounds are reported, we suggest this title is amended.	N/A	Thank you for spotting. We have edit this sentence and now reads 'Table 4 and Table 5 below provide detailed information on the patient and procedure characteristics and methodology for each of the included studies.'

Issue 3

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 34: The text states that BCSP sub-group analyses were ad-hoc in the ADENOMA study. This was not the case as these	This text should be amended to state that BCSP analyses were planned analyses.	N/A	We have used the term ad-hoc to clarify that these analyses were pre-planned opposite to post-hoc. Since this may lead to confusion we have amended the

were planned subgroup analyses as stated in the study protocol reported by Bevan et al (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4751019/pdf/10-1055-s-0041-107900.pdf).			wording and the sentence now reads 'All subgroup analyses reported were pre-planned.'

Issue 4

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 43: Commentary on the meta-analysis by Williet et al does not account for the generation of device used in studies included in the meta-analysis or the failure of the meta-analysis to provide results for a screening/non-screening population. Therefore, the use of this information as part of the current assessment is considered inaccurate. The majority of studies included in the meta-analysis reported by Williet et al report outcomes for the original ENDOCUFF and should be considered outside of the scope of this assessment as the two devices are substantially different from one another. Additionally the study does not provide analyses by screening/non-screening	Discussion regarding Williet et al should be removed from the report. In particular, the reference to a cut-off point above which ENDOCUFF VISION® may not demonstrate value should be removed as this is based on a combination of ENDOCUFF VISION® and ENDOCUFF data and does not differentiate between the screening and non-screening populations.	The cut-off point for ADR is not specific to a sub-population. The manufacturer submission focuses on the screening population, as this is where benefit has been demonstrated for ENDOCUFF VISION® in the ADENOMA study. In this study ENDOCUFF VISION® demonstrated a substantial and significant benefit above standard colonoscopy where the baseline ADR for SC was >50%. This is in excess of the cut-off proposed by Williet et al. Additionally, the conclusions of the Williet study are heavily influenced by original ENDOCUFF data which is outside of the scope of this appraisal.	Thank you for your comment. The manufacturer's submission includes evidence for both a screening and a non-screening population with the focus of the economic model being the screening population. However, the scope is broader including people undergoing colonoscopy for suspected bowel cancer, for the removal of known polyps and for surveillance following previous adenoma removal. As a result evidence on the efficacy of EV for the whole population are relevant. We have amended the report to reflect the fact that Williet 2018 included studies with Endocuff Vision and the older version more accurately. Please note that the proposed cut off for high vs low ADRs is taken by the national audit and not the meta-analysis as follows 'As noted in the national BCSP audit (Lee 2012), there is

population which limits the comparability against the value message submitted for ENDOCUFF VISION®. Using this meta-analysis to suggest a cut-off point for the benefit of ENDOCUFF VISION® is inappropriate. Additionally, the cut-offs proposed do not differentiate between the screening and non-screening population. Further, the evidence used in the meta-analysis for the upper cut-off group is taken from three studies: E-Cap, Van Doorn and Cattau et al. These are considered to be inappropriate for reaching a conclusion regarding the benefit of ENDOCUFF VISION® in centres with baseline ADR of >45% for the following reasons: • Van Doorn – presented data on the original ENDOCUFF which is not included in the scope of this appraisal. Additionally the study was underpowered for the analysis of ADR and is the study given most weight in the meta-analysis. • Cattau et al – this was presented as an abstract only and from the limited			considerable variation in ADR between colonoscopists, ranging from 21.9% to 59.8%. As the audit reports a mean baseline ADR of 46.5%, an ADR above that can be considered as high.' The meta-analysis cut-off is merely a conclusion of that evidence. Finally, the information included in the report that discusses ADR cut-offs is referring to individual colonoscopists' expertise and not average rates such as the >50% ADR rate for the SC cohort in ADENOMA. As far as we are aware the ADENOMA trial has presented ADR analysis looking at the individual user performance without, however, separating to high and low expertise as follows 'There were no differences in individual colonoscopists' ADR between the first 20% and last 20% of procedures.'

information presented it is unknown whether the original ENDOCUFF/ENDOCUFF VISION® was used in the study. Additionally the population (screening/surveillance) is also unclear from the abstract. • E-Cap – The EAC's critical appraisal indicates that the findings of the E-Cap study may not be representative given a potential for bias from a single centre Finally in relation to the proposed cut-off the ADENOMA study showed improvement in ADR in the BCSP against a SC ADR >50%			

Issue 5

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 43: "The meta-analysis by Williet 2018 showed that the ADR was significantly increased in the EVC vs SC group…" As outlined in Issue 4, the majority of studies included in the	This text should be amended or removed to reflect that this meta-analysis does not provide a pooled ADR for ENDOCUFF VISION® only studies.		We have amended the report to highlight the fact that the meta-analysis included studies that have used both EV and the previous generation. This section now reads 'A recently published meta-analysis supports the above findings and input from clinical experts showing that

Williet meta-analysis are not for ENDOCUFF VISION®. Whilst a meta-analysis was conducted for ENDOCUFF VISION® studies, the authors do not appear to report a pooled ADR outcome for ENDOCUFF VISION®.			the effect of high ADR on the efficacy of Endocuff-assisted colonoscopy was noted in the previous version of the device as well (Williet 2018). The meta-analysis, that includes studies using both EV and the previous version, showed that the ADR was significantly increased in the Endocuff-assisted colonoscopy vs. SC group only for operators with low-to-moderate ADRs (<35%). In contrast, this benefit was not reached for operators with high ADRs (>45%).'

Issue 6

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 50: The following statement, regarding non-detection with ENDOCUFF VISION®, is incorrect, "The proportion of undetected adenomas that are low risk, high risk or CRC is assumed to be the same as that for detected adenomas in patients receiving endoscopy with ENDOCUFF VISION®"	The model only applies a non-detection rate for ENDOCUFF VISION® to colonoscopies subject to a learning curve. For these colonoscopies, detection is aligned with the results for standard colonoscopy in the ADENOMA study. All colonoscopies outside this period undertaken with ENDOCUFF VISION® are assumed to have 100% sensitivity.	Clarification is required on the application of non-detection with ENDOCUFF VISION®.	The EAC accepts that the assumption applies only to adenomas missed attributable to the learning curve effect. The report has been amended to make this clear.

Issue 7

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 54: The final sensitivity analysis presented on this page does not have a result reported.	Include sensitivity analysis result	N/A	The EAC now includes a statement that Endocuff Vision is cost incurring at a recall interval of three years for low risk patients.

Issue 8

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 60: The statement that a modification to the model was made in order that "the underlying distribution of adenomas will be the same regardless of colonoscopy use" is incorrect. The model assumes the same distribution of adenomas in the base scenario.	Please clarify the assumptions applied in this scenario analysis.	The base case analysis assumes the underlying distribution of adenomas is equal across both arms of the model.	The EAC accepts that the original statement was misleading; the sponsor's submission does assume the same distribution of adenomas by risk across treatment in comparators in the base case analysis. The EAC implemented a model modification to preserve the same distribution of adenomas across treatment and comparator during sensitivity analysis in which the ADR with Endocuff Vision was reduced. The report has been amended to clarify this point.

Issue 9

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 60: The following text is inaccurate, “In practice it seems likely that smaller adenomas, which are more likely to be low risk, would be more likely to be missed.” Guidelines recommend risk status is defined by both size and number of adenomas detected.	Changing the assumption that the risk of missing an adenoma is dependent on its size is not equivalent to assuming a change in a patients risk profile. The text should reflect that this scenario can only approximate changes in risk status.	Amend proposed in order to reflect guidelines.	The EAC have amended the statement in their report.

Issue 10

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Table 1: Critique of decision problem Population section – EAC Comment “All studies included a higher proportion of men rather than women.”	Rameshshanker 2016 does not report the proportion of male/female participants in the study.	Amend text in line with reported data.	We have amended the report to clarify that this statement is only applicable for studies that reported this information. It now reads ‘With the exception of Rameshshanker 2016 that did not report men to women ratio, all other studies included a higher proportion of men rather than women.’

Issue 11

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Table 1: Cancer diagnosis and management section and patient outcomes section should have subheadings formatted appropriately	N/A	N/A	Thank you we have amended accordingly.

Issue 12

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 20: The following text is inaccurate “531 adult patients were randomised 1:1 in a single-blind RCT comparing EVC to standard colonoscopy.” 534 patients were randomised. 531 patients were analysed.	Amend text to 534 patients were randomised. 531 patients were analysed.	Amend text in line with reported data.	Amended accordingly.

Issue 13

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 21: The following text is inaccurate, “Subgroup analysis in patients with a positive FIT test revealed no significant advantage to EV. “ Patients in the E-CAP study were identified using the FOBT, not FIT.	Amend text to FOBT.	Amend text in line with publication.	Amended accordingly.

Issue 14

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 21: The following text is inaccurate, “Subgroup analysis in patients with a positive FIT test revealed no significant advantage to EV.” There was a significant difference between groups re withdrawal time <0.005	Amend text to reflect statistically significant benefits on withdrawal time.	Amend text in line with reported data.	We have amended accordingly and the sentence now reads ‘With the exception of withdrawal time, subgroup analysis in patients with a positive FOBt revealed no significant advantage to EV.’

Issue 15

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 22 - The following text is inaccurate, “Caecal intubation time was significantly increased in the pre-cuff compared to the cuff periods (1 minute longer, p=0.002) and significantly increased in the post-cuff compared to the cuff period (2 minutes longer, p=0.02), although there were no significant differences between the pre-cuff and post-cuff periods. Similarly, negative colonoscopy time was significantly longer in the pre-cuff compared to the cuff period (12 vs. 8.5 minutes, p<0.001) and significantly longer in the post-cuff compared to the cuff periods (9.75 vs. 8.5 minutes, p=0.05). The highlighted p-value should be 0.002.	Correction of reported p-value.	Amend text in line with reported data.	Thank you we have amended accordingly.

Issue 16

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 23 states “However, ADR (83.67% vs. 55.32%, p=0.004) and SP6 (1.11 vs. 0.6, p=-0.0004) were both significantly increased in the EVC group compared to standard colonoscopy.” The following endpoints were also found to be significant when calculated based on data reported in the publication and submitted by the sponsor: • A significant increase in mean number of polyps per procedure (2.31 vs 1.32, p= <0.001) • Significant increase in mean number of adenomas per procedure (1.94 vs 1.09, p=0.0005)	Additional endpoints should be included in the report text.	Amend text in line with submission.	Thank you for your comment. The included studies narrative section aims to provide an overview of the methodology for each study and main outcomes. Detailed numeric description of each study results is included in tables 9 and 10 were we already list these outcomes for Rameshshanker 2016.

Issue 17

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Table 10 presents the following data in the wrong columns:	Amend text in line with data presented in publications.	Amend text in line with reported data.	Thank you we have amended accordingly.

• E-Cap data presented for small adenomas should be presented under large adenomas. • E-Cap data presented for sessile serrated adenomas should be under large polyp detection rate. • Rameshanker data presented for SSA is data for SSA/polyps. Additionally data is presented as percentages but should be presented as an average • Rameshanker PDR is presented as a percentages but is actually mean number of polyps per patient			

Issue 18

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 48: incomplete sentence "The model."	Either delete text or complete sentence.	N/A	The EAC has deleted the text; this was a typographical error.

Issue 19

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 49: For completeness please include the text linked to the asterisk in figure 2.	Add text as note to figure	N/A	We have added the text linked to the asterisk in figure 2.

Issue 20

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 41: The adverse event search reported on page 41 searched for events reported between 2/2014 and 09/2015. This includes a period before ENDOCUFF VISION® received its CE mark and therefore may return results that are outside the scope of this appraisal.	That the CE mark had not been received for some of the search period should be reflected in the text.	N/A	According to correspondence with the manufacturer the original CE mark was given in September 2014 and was renewed in August 2016. Only 1 of the events was reported in 2014 the rest were reported following the EV CE mark approval. We have amended accordingly to reflect this. The sentence now reads ' All incidents were reported between 2/2014 and 09/2015, with one of the incidents taking place in 2014 and possibly reflecting a version prior to EV official CE mark in September 2014.'

Issue 21

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 33: The text states that "With the exception of the E-Cap RCT that reported unusually high caecal intubation and withdrawal times (approximately 16min and 17-19min, respectively)" This difference was driven by a difference in the definition of withdrawal time in the E-CAP study compared to the other three included studies. This should be reflected in the text.	Please clarify that the withdrawal time measure reported in the E-CAP study differs to that used in the other included studies.	N/A	Thank you for providing this explanation. We have added the following to this section 'Contrary to the other two studies, E-Cap appears to have been included in the calculation of withdrawal time of both positive and negative colonoscopies, which may explain the longer withdrawal time.'

Issue 22

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 53: Without further information on the calculation of the FOBT results calculation it is not possible for the sponsor to evaluate the accuracy of the amend made by the EAC.	None proposed due to limited impact on model results.	N/A	Thank you for your comment.

Please add more rows as required