

**NICE HealthTech Programme**

**Capsule sponge tests for detection of Barrett's oesophagus and early-stage oesophageal cancer and surveillance of Barrett's oesophagus**

**Protocol**

**NIHR Reference Number** – NIHR177652

Version date: 5<sup>th</sup> of March 2026

**1. Name of External Assessment Group (EAG) and project lead**

External Assessment Group

Sheffield Centre for Health and Related Research (SCHARR), University of Sheffield

Project lead: Matt Stevenson

Post held: Professor of Health Economic Modelling

Official address: Health Economic and Decision Science (HEDS), SCHARR, University of Sheffield

Telephone number: [REDACTED]

Fax number: N/A

Email address: [REDACTED]

This report was commissioned through the NIHR Evidence Synthesis Programme as NIHR177652

## **2. Plain English Summary**

People with chronic reflux disease may develop a condition called Barrett's oesophagus, where the cells lining the oesophagus (food pipe) become damaged and change shape. People with chronic reflux disease may receive a test called an endoscopy to check whether they have Barrett's oesophagus. Also, people with Barrett's oesophagus have an increased risk of developing cancer of the oesophagus. Because of this, people diagnosed with Barrett's oesophagus may be offered regular endoscopies to check for cancer or pre-cancer, so that it can be treated earlier. In an endoscopy, a tube with a small camera and a device to collect body cells is inserted through the mouth to the oesophagus. Endoscopies often require sedation and can be uncomfortable. Capsule sponge is a test which is less painful than endoscopy. A capsule sponge is swallowed under clinical supervision but without sedation. Once swallowed, the outside of the capsule dissolves, to release a 'sponge on a thread' which expands. The sponge is then pulled back up, collecting body cells as it exits the mouth. The sponge is sent to a laboratory where it is tested to check whether the person is likely to have Barrett's oesophagus, and also to check for cancerous and pre-cancerous cells. Two capsule sponge tests exist (Cytosponge and EndoSign) although experts believe these give very similar results.

Capsule sponge tests may be used instead of endoscopy to check which people with reflux disease are likely to have Barrett's oesophagus, and also to check which people with Barrett's oesophagus are likely to have cancerous or precancerous cells. People at highest risk of having Barrett's oesophagus, cancer or pre-cancer would then receive an endoscopy, whilst those at lower risk may be able to avoid an endoscopy. This project will summarise research studies assessing the accuracy of using capsule sponge as a first test in place of endoscopy. It will aim to estimate: how many Barrett's oesophagus cases and cancer cases might be missed, and the likely harm caused; how many fewer endoscopies may be needed; benefits to patients due to the easier way of collecting body tissue; possible reduced waiting times; and the likely cost savings for the NHS. These outcomes will be combined in a mathematical model to estimate whether capsule sponge tests represent good value for money for the NHS.

### **3. Decision problem**

#### *3.1 Purpose of the decision to be made*

The objective of this assessment is to appraise the clinical and cost-effectiveness of capsule sponge tests within their indication for the detection of Barrett's oesophagus and early-stage oesophageal cancer in people with gastro-oesophageal reflux disease and risk factors, and for surveillance in people who have a known diagnosis of Barrett's oesophagus.

#### *3.2 Definition of the interventions*

Two capsule sponge tests to be assessed are:

- EndoSign (Cyted Health)
- Cytosponge (Medtronic).

Clinical opinion provided to the External Assessment Group (EAG) at the scoping workshop suggests that very similar results are produced by both tests and that it is likely that results from one test are generalisable to the other.

#### *Capsule sponge tests*

The relevant intervention is the capsule sponge test (EndoSign or Cytosponge), which is a cell collection device used with biomarker testing to check for abnormal cells in the oesophagus. These small capsule-shaped devices are swallowed under clinical supervision, but without the need for sedation. The capsule is dissolvable and when swallowed, expands (within 7 minutes) into a small, rough-textured sponge in the person's stomach. The sponge is then extracted via a thread attached to it, collecting some of the cells lining the oesophagus. The sponge is then placed in a fixative, and this sample is shipped using a secure courier network to a single central laboratory (Cyted Health's histopathology laboratory in Huntingdon, UK) which carries out histological staining and biomarker tests.

#### *Testing schedules*

If appropriate, the impact of different testing schedules will be considered, including repeat capsule sponge testing only, and alternating capsule sponge testing and surveillance endoscopy.

#### *Details of EndoSign test*

The EndoSign technology consists of the EndoSign cell collection device and the EndoSign preservation kit. The former is CE-marked and UKCA marked as a Class I medical device. The latter is CE-marked and UKCA marked as a Class A in-vitro diagnostic. The diagnostic assay is performed by Cyted Health's histopathology laboratory. EndoSign also has a proprietary applicator to position the capsule on the back of the person's tongue. EndoSign's capsule is

made from hydroxypropyl methylcellulose and the sponge is made from polyurethane. The company provides training to all healthcare professionals administering the technology.

EndoSign is contraindicated for use in people with symptoms of dysphagia or other swallowing disorders, people with a previous endoscopic therapy or who have had a surgical procedure involving the stomach or oesophagus, people with a known or suspected anatomic abnormality of the oesophagus or stomach, women who are or may be pregnant, people with known or suspected portal hypertension, gastric or oesophageal varices and people on anti-thrombotic drugs which cannot be temporarily discontinued before and after the procedure. In England, EndoSign is currently used in 18 sites for the detection of Barrett's oesophagus and in 30 sites for surveillance of Barrett's oesophagus.

#### *Details of Cytosponge test*

The Cytosponge technology is CE-marked as a Class I medical device. It is not known to the EAG whether this regulatory approval covers both the cell collection device and the preservation kit. Samples collected with Cytosponge are analysed by Cytel Health's laboratory. According to publicly available information, Cytosponge's capsule is made from vegetarian gelatine and the sponge is made from polyethylene. The company has a training pathway for Cytosponge users in the UK.

Cytosponge is contraindicated for use in people with symptoms of dysphagia or history of swallowing disorders, people with known or suspected anatomical abnormalities of the oesophagus or stomach, people who have undergone oesophageal or gastric dilation, ablation, biopsy, mucosal resection or other invasive medical procedures within the previous two months, as well as women who are or may be pregnant. Cytosponge should also not be used in people with known or suspected portal hypertension and/or gastric or oesophageal varices and people on anti-thrombotic drugs that cannot be temporarily discontinued. Cytosponge has been used in 6 NHS sites in the past 24 months, with 58 sites having received training to use the device over the past 5 years.

#### *Laboratory assessment of capsule sponge tests*

During laboratory assessment, histological staining and two biomarker tests are conducted on all samples, and the diagnostic results shared with the requesting clinician within 14 working days from the day of sample receipt:

- Haematoxylin and eosin (H&E) staining to detect:
  - Gastric cells: Quality control to show that the capsule reached the stomach

- Cellular atypia: Positivity indicates inflammation, dysplasia or malignant changes
- Trefoil factor family 3 (TFF3) antibody test: Positivity indicates intestinal metaplasia and presence of Barrett's oesophagus; when used in surveillance this would be a quality control as all samples would be expected to be positive
- Tumour protein 53 (p53) test: Positivity indicates dysplasia or malignant changes.

*Follow-up options in the context of detecting Barrett's oesophagus:*

Based on the diagnostic results, a number of follow-up options are available:

- Atypia (definite or of uncertain significance) and/or abnormal or equivocal p53: referral to an urgent endoscopy.
- TFF3 positive for intestinal metaplasia, with normal p53 and no atypia, indicating presence of Barrett's oesophagus: referral for routine endoscopy for confirmation.
- TFF3 negative (or equivocal) for intestinal metaplasia, with normal p53 and no atypia: manage according to symptoms with appropriate safety netting.
- Insufficient sample: repeat testing or an endoscopy as soon as feasible (within 3 months).

*Follow-up options in the context of surveillance of Barrett's oesophagus:*

Based on the diagnostic results, a number of follow-up options are available:

- Atypia (definite or of uncertain significance) and/or abnormal or equivocal p53: referral to an urgent endoscopy.
- TFF3 positive with normal p53 and no atypia: clinical risk factors can be used to plan an appropriate surveillance interval (the key clinical diagnostic accuracy paper<sup>1</sup> advocates that, following a biomarker negative capsule sponge test, patients may be subdivided into moderate and low risk depending on the maximal or circumferential length of the Barrett's oesophagus and the age and sex of the patient).
- TFF3 negative (or equivocal) for intestinal metaplasia, with normal p53 and no atypia: clinical judgement based on previous results and the length of the Barrett's oesophagus segment is needed to decide whether repeat testing is needed.
- Insufficient sample: repeat testing or an endoscopy as soon as feasible (within 3 months).

### 3.3 *Populations and relevant subgroups*

#### *Populations*

The population of interest for this assessment are:

- People presenting to their GP with gastro-oesophageal reflux disease (GORD) that persists despite recommended lifestyle and pharmacological management strategies, and who have multiple risk factors and do not have dysphagia or weight loss
- People with diagnosed Barrett's oesophagus with intestinal metaplasia and no dysplasia who are on a surveillance programme to check for cancer or pre-cancer/dysplasia.

In Barrett's oesophagus, some normal cells of the lower part of the oesophagus (distal squamous epithelium) have been replaced by cells like those lining the stomach and bowel (metaplastic columnar epithelium). This area has to be clearly visible endoscopically (more than 1 cm in length) above the gastro-oesophageal junction (the area where the oesophagus connects to the stomach) and confirmed histopathologically from biopsies. Barrett's oesophagus is estimated to affect 1 to 2% of the adult population.

Chronic GORD is a risk factor for developing Barrett's oesophagus. People with Barrett's oesophagus have a higher risk of developing oesophageal adenocarcinoma. Barrett's oesophagus can be classified as short-segment (less than 3cm) or long-segment (3cm or longer). It can also be staged according to level of dysplasia (non-dysplastic, indefinite, low-grade dysplasia, high-grade dysplasia, carcinoma).

### *Subgroups*

Where evidence allows, the following subgroups may be considered:

- People with short (less than 3 cm) and long (more than 3 cm) segments of Barrett's oesophagus
- People at a low or high risk of developing dysplasia or oesophageal adenocarcinoma (e.g., based on male sex, older age, socioeconomic status or family history of oesophageal adenocarcinoma)
- People at low, moderate or high risk of developing dysplasia or oesophageal adenocarcinoma based on the results of a capsule sponge test and clinical factors as described in Tan *et al.* 2025<sup>1</sup>
- People having surveillance after endoscopic therapy (in whom Cytosponge is not contraindicated according to the device manufacturer).

### 3.4 *Place of the intervention in the treatment pathway*

Barrett's oesophagus is currently diagnosed via endoscopy, which may be offered to people with GORD and particular risk factors.

People with Barrett's oesophagus are currently recommended to undergo surveillance via upper gastrointestinal endoscopy with biopsy, to check for cancer or pre-cancer. Endoscopy is usually carried out in secondary care and includes sedation. Details of current surveillance approaches are covered under Section 3.5.

The capsule sponge test could be used as a less invasive alternative to endoscopy in the following two scenarios:

- (i) Detection of Barrett's oesophagus in people with multiple risk factors and GORD that persists despite recommended lifestyle and pharmacological management; and
- (ii) Surveillance of Barrett's oesophagus. Depending on the capsule sponge test results, people would be triaged to endoscopy or not. The relevant settings for the capsule sponge test are community, primary, secondary and specialist care.

This assessment will not consider the use of capsule sponge tests for population screening in people without risk factors and persistent GORD.

### 3.5 *Relevant comparators*

The comparator for this appraisal is upper gastrointestinal endoscopy with biopsy, for diagnosis or surveillance of Barrett's oesophagus.

For detection of Barrett's oesophagus, the NICE guidelines on GORD (NICE clinical guideline (CG) 184)<sup>2</sup> recommends that endoscopy should be considered for people with GORD depending on their preferences and risk factors (e.g. male sex, long duration of symptoms, increased frequency of symptoms, previous oesophagitis, previous hiatus hernia, oesophageal stricture or oesophageal ulcers). The British Society of Gastroenterology (BSG) guideline on Barrett's oesophagus<sup>3</sup> recommends that endoscopy should be considered for people with chronic GORD symptoms and multiple risk factors (at least three of: age over 50, White ethnicity, male sex or obesity).

For surveillance of Barrett's oesophagus, the BSG guideline on Barrett's oesophagus<sup>3</sup> and NICE guidelines on Barrett's oesophagus (NG 231)<sup>4</sup> recommend surveillance via upper gastrointestinal endoscopy with biopsy to check for cancer or pre-cancer. In the surveillance context, surveillance frequencies are recommended as follows:

- Barrett's oesophagus shorter than 3 cm with intestinal metaplasia: every 3-5 years
- Barrett's oesophagus that is 3 cm or longer: every 2-3 years

- Barrett's oesophagus shorter than 3 cm without intestinal metaplasia or dysplasia: repeat endoscopy to confirm the diagnosis, then discharge from surveillance in the absence of metaplasia or dysplasia.

Surveillance approaches should also consider:

- presence of dysplasia (stable non-dysplastic Barrett's oesophagus may be at low risk of progression to cancer)
- the person's risk factors (e.g. male sex, older age, length of segment)
- the person's individual preference.

If dysplasia is found, high-grade dysplasia is recommended to be treated via endoscopic resection and endoscopic ablation, while endoscopic ablation may be an option for low-grade dysplasia.

### 3.6 Outcomes

Relevant outcomes include the following. Outcomes from the NICE scope have been grouped into clinical review outcomes, model input parameters and model outcomes.

*Primary outcomes from the clinical review:*

- Diagnostic accuracy of a) capsule sponge tests and b) capsule sponge tests plus clinical factors for detecting:
  - intestinal metaplasia i.e. presence of Barrett's oesophagus (via TFF3 biomarker)
  - high-grade dysplasia, any dysplasia or cancer (via p53 biomarker and H&E staining for cellular atypia)
- Diagnostic yield of capsule sponge tests for detecting intestinal metaplasia, high-grade dysplasia, any dysplasia, cancer or other pathology
- For comparative studies (capsule sponge vs. no capsule sponge): Proportion diagnosed with Barrett's oesophagus or dysplasia/cancer per group.

*Secondary outcomes and model parameters: Studies included in the clinical review will be checked for the outcomes below, and this will be supplemented by a targeted review of specific outcomes if required for the model:*

- Adverse events
- Time to intervention following an adverse event
- Health-related quality of life
- Patient acceptability
- Anxiety attributed to being on a waiting list

- Healthcare professional acceptability
- Procedure uptake
- Procedure success
  - Proportion of capsules successfully swallowed
  - Proportion of capsules successfully swallowed and retrieved via the thread
- Time to do the procedure
- Repeat procedures due to insufficient sample collected
- Proportion of samples successfully assessed in a laboratory
- Follow-up urgent endoscopies needed
- Follow-up non-urgent (routine) endoscopy needed
- Reduction in upper GI endoscopy wait times
- Cancer-related and all-cause mortality or survival

*Costs and resource use parameters:*

- Cost of the technology (including the device and laboratory assessment costs)
- Cost of follow-up upper GI endoscopy
- Cost of treatment and management
- Cost of training
- Staff time at different specialisms and levels of pay
- Staff cost at different specialisms and levels of pay
- Health service use at different settings
- Cost of health service use at different settings

*Output from the model:*

- The primary model output will be the cost-effectiveness of interventions. This will be expressed in terms of incremental cost per quality-adjusted life year (QALY) gained. Costs will be considered from an NHS and Personal Social Services (PSS) perspective.

Secondary outputs will include estimates of:

- The number of true positive, true negative, false positive and false negative diagnoses due to the use of capsule sponge tests
- The number of additional cancers caused by a delayed diagnosis due to false negative diagnoses
- The estimated numbers of endoscopies associated with each strategy explored
- The potential reduction in the waiting list and/or time to diagnosis due to the removal of patients from the waiting list for endoscopy due to a negative capsule sponge test

- QALY losses due to AEs associated with endoscopic or capsule sponge procedures

### 3.7 *Issues for consideration*

#### *The generalisability of results for Cytosponge and EndoSign.*

The EAG is aware of a high-quality diagnostic study estimating the sensitivity and specificity of capsule sponge compared with endoscopy. However, this study appears to make no distinction between the diagnostic accuracy of Cytosponge and EndoSign. As such, there are no publicly available individual diagnostic accuracy data in order to compare the clinical efficacy of the two capsule sponge interventions. If individual data are not available, then the two tests may need to be considered homogeneous for diagnostic accuracy.

In pilot data from NHS England (NHSE) the capsule sponge was restricted to Cytosponge, and thus this source of real-world evidence is not available for EndoSign. If no such data can be found for EndoSign then the two tests may need to be considered homogeneous for parameter values, such as patient perception, adverse events, and the number of repeat tests reported in the NHSE pilot.

### 3.8 *Areas that are outside the scope of the evaluation and therefore do not require any detailed assessment*

Areas which will be excluded from this appraisal:

- The use of capsule sponge tests as a population screening tool in people without risk factors and persistent GORD.

## **4. Report methods for clinical systematic review**

### *4.1 Overview of systematic review methodology*

Systematic reviews of clinical evidence will be undertaken. The review will follow the general principles recommended in CRD's guidance,<sup>5</sup> the PRISMA statement,<sup>6</sup> and the NICE Methods Manual.<sup>7</sup>

### *Inclusion criteria*

The inclusion criteria for the review will be in line with the decision problem defined in the NICE scope. These are detailed in the sections below.

### *4.2 Population and subgroups*

The relevant population comprises:

- People presenting to their GP with GORD that persists despite recommended lifestyle and pharmacological management strategies, who have multiple risk factors and do not have dysphagia or weight loss (studies in people with GORD who do not present via a GP will also be included in the review, and generalisability of such studies will be considered)
- People with diagnosed Barrett's oesophagus with intestinal metaplasia and no dysplasia who are on a surveillance programme to check for cancer or pre-cancer/dysplasia.

Studies will be excluded if the population is contraindicated according to the device manufacturer (e.g. people with a previous endoscopic therapy in the case of EndoSign, or people who have undergone esophageal or gastric dilation, ablation, biopsy, mucosal resection or other invasive medical procedures within the previous two months in the case of Cytosponge). Studies that recruit a wider population will be included where separate data are reported for a relevant population.

Where evidence allows, the following subgroups may be considered:

- People with short (less than 3 cm) and long (more than 3 cm) segments of Barrett's oesophagus
- People at a low or high risk of developing dysplasia or oesophageal adenocarcinoma (e.g., based on male sex, older age, socioeconomic status or family history of oesophageal adenocarcinoma)
- People at low, moderate or high risk of developing dysplasia or oesophageal adenocarcinoma based on the results of a capsule sponge test and clinical factors as described in Tan *et al.* 2025<sup>1</sup>

- People having surveillance after endoscopic therapy (in whom Cytosponge is not contraindicated according to the device manufacturer).

#### 4.3 *Interventions*

The following two capsule sponge tests identified in the NICE scope will be included:

- EndoSign
- Cytosponge.

Where data allow, data will be included for a) capsule sponge tests alone and b) capsule sponge tests plus clinical factors.

#### 4.4 *Comparators*

##### *Comparator for the assessment*

The relevant comparator for the assessment is high-resolution white light upper gastrointestinal endoscopy with histopathological assessment of biopsy samples. Endoscopy with biopsy is also the relevant comparator for comparative studies.

##### *Relevant reference standard tests*

For diagnostic accuracy studies, endoscopy is the preferred reference standard. Studies in which all patients received endoscopy will be prioritised. Studies using other reference standards (such as clinical follow-up), and studies in which only a subset received endoscopy will be considered for inclusion if there are limited data for any population group.

Diagnostic accuracy data for endoscopy (the comparator for the assessment) will not be systematically reviewed. If required as a model parameter, data will be sought in line with other modelling parameters; that is, from studies meeting the inclusion criteria for the clinical review and from other papers known to the EAG, supplemented by a targeted search if required.

#### 4.5 *Outcomes*

Relevant outcomes for the clinical review include the following:

##### *Primary outcomes from the clinical review:*

- Diagnostic accuracy of a) capsule sponge tests and b) capsule sponge tests plus clinical factors for detecting:
  - intestinal metaplasia i.e. presence of Barrett's oesophagus (via TFF3 biomarker)

- high-grade dysplasia, any dysplasia or cancer (via p53 biomarker and H&E staining for cellular atypia)
- Diagnostic yield of capsule sponge tests for detecting intestinal metaplasia, high-grade dysplasia, any dysplasia, cancer or other pathology
- For comparative studies (capsule sponge vs. no capsule sponge): Proportion diagnosed with Barrett's oesophagus or dysplasia/cancer per group.

*Secondary outcomes from the clinical review (to be summarised in a brief narrative review):*

- Adverse events
- Time to intervention following an adverse event
- Health-related quality of life
- Patient acceptability
- Anxiety attributed to being on a waiting list
- Healthcare professional acceptability
- Procedure uptake
- Procedure success
  - Proportion of capsules successfully swallowed
  - Proportion of capsules successfully swallowed and retrieved via the thread
- Time to do the procedure
- Repeat procedures due to insufficient sample collected
- Proportion of capsule sponge tests that are appropriately assessed in a laboratory
- Follow-up urgent endoscopies needed
- Follow-up non-urgent (routine) endoscopy needed
- Reduction in upper GI endoscopy wait times
- Cancer-related and all-cause mortality or survival

#### 4.6 *Types of clinical evidence required and study designs*

This section summarises the types of evidence which will be sought from the clinical evidence review and the main study designs for each evidence type. These will be incorporated into the health economic model in order to inform the estimated clinical effectiveness and cost-effectiveness of the tests.

Study designs to be sought within the clinical review:

- Comparative studies: Initially, randomised controlled trials (RCTs) comparing capsule sponge testing to endoscopy will be sought. If there is insufficient evidence from RCTs, non-randomised controlled studies will be sought.

- Diagnostic test accuracy: Diagnostic accuracy studies will be included (that is, comparing capsule sponge testing to a relevant reference standard). Cohort studies (in which patients are recruited before diagnosis) will be prioritised over case-control (two-gate) studies (which compare known cases versus controls).
- Any relevant systematic reviews identified during study selection will be used to check for additional studies, and used for data extraction, where relevant.

#### *Date, language and publication type limits*

Studies not published in the English language will be included if sufficient information on the population, intervention, comparator, outcomes and study design (PICOS) can be extracted from non-English language full-texts, or from an existing English language abstract. Potentially relevant studies excluded on the basis of language will be listed separately. Non-peer-reviewed reports or abstracts will only be included if the data are presented in a succinct and accessible manner (for example, a manuscript prepared for submission to a journal), if sufficient methodological details are reported to allow critical appraisal of the study quality, and if results are reported in sufficient detail.

#### 4.7 *Search strategy*

The search strategy for the systematic review will comprise the following main elements:

- Searching of electronic databases, registers and websites
- Contact with experts in the field
- Scrutiny of bibliographies of retrieved papers and existing systematic reviews
- Information provided by the companies

The databases, trial registers and websites that will be searched include the following:

- MEDLINE and MEDLINE in Process (via Ovid)
- EMBASE (via Ovid)
- Cochrane Database of Systematic Reviews (via Wiley)
- Cochrane Central Register of Controlled Trials (via Wiley)
- HTA Database of the International Network of Agencies for Health Technology Assessment (INAHTA)
- WHO International Clinical Trials Registry Platform
- TRIP Pro Database
- ECRI Guidelines Trust

Trials and conference abstracts from EMBASE will be screened separately from published journal articles. Additional searches will also be conducted of recent meetings of the following conference series:

- World Congress of Gastroenterology (WCOG)
- European Society of Gastrointestinal Endoscopy (ESGE)
- Cambridge Symposium on Oesophageal Cancer
- International Society for Diseases of the Esophagus (ISDE)

Search terms will include capsule sponge and both product names and any alternative names for each of the intervention tests, combined with search terms for the condition of interest (Barrett's oesophagus). We will base our search string on that used by Health Technology Wales in their recent Topic Exploration Report on Capsule sponge devices to detect Barrett's oesophagus and early-stage oesophageal cancer (TER568).<sup>8</sup>

A draft Embase search string is provided in Appendix 9.1; following agreement with clinical experts, this will be translated for each of the databases listed above. A simplified version of this string will be used for a representative selection of sources of unpublished literature to include INAHTA, TRIP Pro and the ECRI Guidelines Trust. Reference lists of included papers, as well as existing systematic reviews, will be assessed for additional relevant studies. Where necessary and where time allows, authors of eligible studies will be contacted for further information. No limits relating to date, language or study design will be applied at the searching stage.

#### 4.8 *Study selection and data extraction strategy*

##### *Study selection*

The titles and abstracts of records retrieved by the search strategy will be deduplicated, then assessed against the inclusion criteria for the review, and irrelevant records will be excluded. The full text of remaining records will be obtained and assessed against the inclusion criteria. Study selection will be conducted by one reviewer. Any studies which give rise to uncertainty will be reviewed by a second reviewer with involvement of a third reviewer when necessary. A 10% sample (or 100 records, whichever is larger) of the records retrieved by electronic searches will be checked by a second reviewer early in the process to ensure consistency, and any discrepancies will be discussed in order to check adherence to the inclusion criteria. Studies examined at full text stage will be checked for inclusion by two reviewers.

### *Data extraction*

A data extraction form will be constructed, for example in Microsoft Excel or Google Sheets. It may be necessary to use different forms for different study designs.

Data will be extracted by one reviewer and checked by a second reviewer. Any disagreements will be resolved through discussion and consultation with a third reviewer where necessary. If time allows, attempts will be made to contact authors for any missing data that are considered essential to the review. Data from multiple publications of the same study will be extracted as a single study.

### 4.9 *Quality assessment strategy*

Studies will be assessed using quality assessment tools relevant to the study design. Tools may be adapted or abbreviated to the specifics of this review, due to time and resource constraints.

For studies that use an RCT design, quality will be assessed using version 2 of the Cochrane Risk of Bias tool (RoB2).<sup>9</sup> For the review of diagnostic test accuracy, the QUADAS-3 tool<sup>10</sup> will be used. Studies with other designs will be assessed using quality appraisal tools appropriate to their specific study design.

Studies will be quality assessed by one reviewer, with scores checked by a second. Any disagreements will be resolved through discussion and consultation with a third reviewer where necessary. The impact of the quality of studies on the evidence base will be evaluated through sensitivity analyses in meta-analysis, or through narrative synthesis of the results.

### 4.10 *Methods of analysis/synthesis*

Studies will be presented according to key characteristics such as population, test, testing schedules (if data allow), comparators, outcomes, and study design, as well as according to the pre-specified subgroups where data permit. A narrative synthesis will be conducted. Any comparisons will acknowledge clinical, methodological and statistical heterogeneity.

Where sufficient data exist, pooled estimates of diagnostic accuracy (sensitivity and specificity) will be estimated using a bivariate meta-analysis model to account for the correlation between sensitivity and specificity.<sup>11</sup> A random-effects model will be used to account for the heterogeneity between studies that is generally expected in diagnostic accuracy studies.<sup>12</sup> Reasons for the heterogeneity in sensitivity and specificity between studies may be explored using meta-regression and/or subgroup analyses. Analyses will be conducted in the R software environment using a suitable Markov Chain Monte Carlo (MCMC) sampler such as JAGS.<sup>13</sup>

Convergence of the MCMC sampling will be assessed using the Gelman-Rubin convergence statistics<sup>14</sup> and trace plot inspection. Results will be displayed as forest plots and summary receiver operating characteristic plots with 95% credible intervals and 95% prediction intervals for sensitivity and specificity.

Statistical synthesis of clinical outcomes will also be conducted, if appropriate.

## **5. Report methods for synthesising evidence of cost effectiveness**

### *5.1 Identifying and systematically reviewing published cost-effectiveness studies*

A systematic review of the existing literature assessing the cost-effectiveness of the tests will be undertaken.

The search strategy will comprise the following main elements:

- Searching of electronic databases
- Contact with experts in the field
- Scrutiny of bibliographies of retrieved papers
- Information provided by the companies.

The databases that will be searched include the following:

- MEDLINE and MEDLINE in Process (via Ovid);
- EMBASE;
- EconLit

Cost effectiveness studies will be identified using the NHS EED search filter and studies of health-related quality of life will be identified using the specificity-maximising filter (FSF3) by Arber *et al.*<sup>15</sup> In addition, relevant cost papers identified from the clinical effectiveness searches will be included in the economic review.

A draft search strategy for MEDLINE is reproduced below – this will be translated as appropriate for the other databases.

### *5.2 Evaluation of previously published cost effectiveness analyses*

Only full economic evaluations published in English addressing the cost-effectiveness of capsule sponge tests will be critiqued. This will include a summary of the strengths and limitations of each study, the conclusions and the generalisability of the publication to the

decision problem. The methods employed and the data sources used to populate the model may inform structural assumptions and parameter values for the EAG model.

### 5.3 *Construction of the health economic model*

The economic analyses will be undertaken in line with the NICE Reference Case.<sup>7</sup> The model will estimate the incremental cost effectiveness ratio (ICER) defined as the cost per QALY gained (or yielded) for each test versus the comparator(s) over a lifetime horizon from the perspective of the UK NHS and personal social services. Results will also be presented in terms of either net monetary benefit (NMB) or net health benefit (NHB) (whichever is deemed most useful for the NICE Appraisal Committee) to remove potential confusion in the interpretation of cost-effectiveness should QALYs be yielded by the interventions.

Secondary outcomes (described in Section 3.6) will also be presented. Modelling assumptions will be drawn from the literature, supplemented with clinical expert opinion. Health-related quality of life data identified from the systematic review of clinical evidence, from the identified cost-effectiveness papers, or from a targeted search of reviews of quality of life in patients with Barrett's oesophagus or oesophageal cancer will inform the utility values in the model. Costs will be derived from national sources (for example, NHS Reference Costs,<sup>16</sup> the British National Formulary,<sup>17</sup> the Commercial Medicines Unit electronic Market Information Tool<sup>18</sup>), relevant literature and data provided by the manufacturers and other stakeholders.

Based on clinical advice provided at the scoping workshop and noting that a recent diagnostic accuracy study<sup>1</sup> did not distinguish between the Cytosponge and the EndoSign capsule sponge tests, the EAG will not differentiate between the two tests in terms of diagnostic accuracy unless clear evidence is published in the course of the appraisal that this assumption is incorrect. This assumption is also likely to apply to adverse events, although the costs may differ between the two devices.

Two sets of analyses will be produced to match the populations within the scope (those being diagnosed and those under surveillance). Each will report ICERs and NMBs or NHBs which are anticipated to differ between the populations. Probabilistic sensitivity analysis will be undertaken using Monte Carlo sampling. The uncertainty around each parameter will be represented using a probability distribution, with correlation between parameters maintained if identified. Decision uncertainty will be presented using cost-effectiveness planes and cost-effectiveness acceptability curves. Deterministic sensitivity analysis will be undertaken to explore the sensitivity of the results to variations in specific input parameters. Scenario analyses

will be presented to explore the impact of alternative assumptions and evidence sources. Results will be presented for perceived important subgroups for which sufficient evidence exists.

A number of approaches will be used to ensure the credibility of the health economic model, including:

- Ensuring that the model is consistent with the NICE Reference Case and published checklists for economic evaluations/models.
- Checking model implementation. This will likely take the form of the two modellers on the team checking the work of the other modeller.
- Ensuring the accuracy of model input parameters against their original sources.
- Checking the appropriateness of model input parameters and assumptions with clinical experts.
- Checking the face validity of the model predictions with clinical experts.

## **6. Handling information from the companies**

All data submitted by the manufacturers/sponsors will be considered if received by the EAG no later than date stated by NICE. Data arriving after this date may not be considered.

If the data meet the inclusion criteria for the review, they will be extracted and quality assessed in accordance with the procedures outlined in this protocol.

Any ‘academic in confidence’ data provided by a manufacturer and specified as such will be highlighted in **yellow and underlined** in the assessment report. Any ‘commercial in confidence’ data provided by a manufacturer and specified as such will be highlighted in **blue and underlined** in the assessment report (followed by an indication of the relevant company name e.g., in brackets). Any confidential data used in the cost-effectiveness model will also be highlighted.

A version of the economic model with confidential information redacted or replaced with dummy data will be provided.

## **7. Competing interests of authors**

None

## **8. Timetable/milestones**

<b>Milestone</b>	<b>Date to be completed</b>
------------------	-----------------------------

Final date for manufacturer/sponsor data submissions	24 March 2026
Progress report	To be confirmed
Draft assessment report and executable economic model sent to NICE	26 June 2026
Final report and executable economic model sent to NICE	21 August 2026

## 9. Appendices

### 9.1 Draft search strategy 1 – SLR of clinical evidence

#### Draft Embase search strategy

Embase <1974 to 2026 Week 03>

- 1 Barrett Esophagus/ 22106
- 2 (barrett\* adj3 (esophag\* or oesophag\* or epitheli\* or metaplasia\* or syndrome\* or surveillanc\*)).tw,kf. 20143
- 3 intestinal metaplasia/ 11589
- 4 exp esophagus tumor/ 124935
- 5 ((esophag\* or oesophag\*) adj3 (cancer\* or neoplasm\* or lesion\* or tumo?r\* or carcinoma\* or adenocarcinoma\* or adenoma\* or sarcoma\* or malignan\*)).tw,kf. 112110
- 6 exp Gastroesophageal Reflux/ 91977
- 7 (gastro-oesophag\* reflux\* or gastrooesophag\* reflux\* or GORD or gastro-esophag\* reflux\* or gastroesophag\* reflux\* or GERD).tw,kf. 59438
- 8 ((acid or acidic or gastr\* or esophag\* or oesophag\*) adj3 reflux\*).tw,kf. 63883
- 9 exp Esophagitis/ 53270
- 10 (esophagitis or oesophagitis).tw,kf. 37413
- 11 esophagus dysplasia/ 1376
- 12 ((esophag\* or oesophag\* or barrett\*) adj3 dysplasia\*).tw,kf. 3618
- 13 (esophag\* or oesophag\* or barrett\*).tw,kf. and dysplasia\*.kf. 1239
- 14 (esophag\* or oesophag\* or barrett\*).tw,kf. and dysplasia/ 7069
- 15 or/1-14 281358
- 16 Esophagus/ 60833
- 17 (esophagus or oesophagus or esophageal or oesophageal or barrett\*).tw,kf. 286082
- 18 or/16-17 297808
- 19 precancer/ 28463
- 20 early cancer diagnosis/ 18796
- 21 or/19-20 46847
- 22 18 and 21 2328
- 23 ((precancer\* or pre-cancer\*) adj3 (barrett\* or esophag\* or oesophag\*)).tw,kf. 545
- 24 ((cancer\* or neoplasm\* or lesion\* or tumo?r\* or carcinoma\* or adenocarcinoma\* or adenoma\* or sarcoma\* or malignan\*) adj3 (screen\* or diagnos\* or detect\*) adj3 (barrett\* or esophag\* or oesophag\*)).tw,kf. 5437
- 25 22 or 23 or 24 7691
- 26 15 or 25 281532
- 27 Trefoil Factor-3/ 1588
- 28 ("trefoil factor 3" or TFF3 or "TFF-3" or "TFF 3").tw,kf. 1598
- 29 (intestinal adj2 trefoil factor).tw,kf. 312
- 30 (capsule adj3 (sponge\* or balloon\* or swallow\*)).tw,kf. 1025
- 31 (sponge adj3 (string\* or cytolog\* or test\*)).tw,kf. 275
- 32 ((esophag\* or oesophag\*) adj3 (sponge\* or string\*)).tw,kf. 163
- 33 (((esophag\* or oesophag\*) adj3 cell collection device\*) or OCCD or ECCD).tw,kf,my,dq. 145
- 34 esophageal cell sampling device/ 235
- 35 ((esophag\* or oesophag\*) adj3 cell sampling device\*).tw,kf. 7
- 36 ((nonendoscop\* or non-endoscop\*) adj3 (screen\* or diagnos\* or detect\* or test\* or surveillanc\* or cytolog\*)).tw,kf. 213
- 37 (minimally invasive and (nonendoscop\* or non-endoscop\*)).tw,kf. 133
- 38 or/27-37 4160
- 39 26 and 38 758

- 40 "sponge on a string".tw,kf. 14  
 41 cytosponge\*.tw,kf. 218  
 42 endosign\*.tw,kf. 13  
 43 cytoprime\*.tw,kf. 2  
 44 esophacap\*.tw,kf. 24  
 45 esocheck\*.tw,kf. 54  
 46 or/40-45 295  
 47 (exp Barrett esophagus/di or exp \*esophagus tumor/di or exp gastroesophageal reflux/di or exp esophagitis/di or esophagus dysplasia/di) and sponge\*.tw,kf. 38  
**48 39 or 46 or 47 825**

## 9.2 Draft search strategy 2 – SLR of economic evidence

Ovid MEDLINE(R) ALL <1946 to February 06, 2026

- 1 Barrett Esophagus/ 9151  
 2 (barrett\* adj3 (esophag\* or oesophag\* or epitheli\* or metaplasia\* or syndrome\* or surveillanc\*).tw,kf. 11248  
 3 1 or 2 12561  
 4 exp Esophageal Neoplasms/ 65139  
 5 ((esophag\* or oesophag\*) adj3 (cancer\* or neoplasm\* or lesion\* or tumo?r\* or carcinoma\* or adenocarcinoma\* or adenoma\* or sarcoma\* or malignan\*).tw,kf. 76501  
 6 4 or 5 90429  
 7 Esophagus/ 45965  
 8 (esophagus or oesophagus or esophageal or oesophageal or barrett\*).tw,kf. 198084  
 9 7 or 8 207301  
 10 Precancerous Conditions/ 30686  
 11 "Early Detection of Cancer"/ 46900  
 12 10 or 11 76590  
 13 9 and 12 3136  
 14 ((precancer\* or pre-cancer\*) adj3 (barrett\* or esophag\* or oesophag\*).tw,kf. 337  
 15 ((cancer\* or neoplasm\* or lesion\* or tumo?r\* or carcinoma\* or adenocarcinoma\* or adenoma\* or sarcoma\* or malignan\*) adj3 (screen\* or diagnos\* or detect\*) adj3 (barrett\* or esophag\* or oesophag\*).tw,kf. 3411  
 16 3 or 13 or 14 or 15 16631  
 17 Economics/ 27557  
 18 exp "costs and cost analysis"/ 285520  
 19 Economics, Dental/ 1922  
 20 exp economics, hospital/ 26422  
 21 Economics, Medical/ 9323  
 22 Economics, Nursing/ 4015  
 23 Economics, Pharmaceutical/ 3176  
 24 (economic\$ or cost or costs or costly or costing or price or prices or pricing or pharmaco-economic\$).ti,ab. 1286818  
 25 (expenditure\$ not energy).ti,ab. 42940  
 26 value for money.ti,ab. 2507  
 27 budget\$.ti,ab. 41447  
 28 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 1462718  
 29 ((energy or oxygen) adj cost).ti,ab. 5275  
 30 (metabolic adj cost).ti,ab. 1988  
 31 ((energy or oxygen) adj expenditure).ti,ab. 32366  
 32 29 or 30 or 31 38484  
 33 28 not 32 1453737  
 34 letter.pt. 1326140

35 editorial.pt. 748225  
36 historical article.pt. 376719  
37 or/34-36 2429873  
38 33 not 37 1410734  
39 exp animals/ not humans/ 5422940  
40 38 not 39 1319970  
41 bmj.jn. 94814  
42 "cochrane database of systematic reviews".jn. 17327  
43 health technology assessment winchester england.jn. 1735  
44 or/41-43 113876  
45 40 not 44 1312724  
46 Quality-Adjusted Life Years/ 18918  
47 (quality adjusted or adjusted life year\$.ti,ab,kf. 31907  
48 (qaly\$ or qald\$ or qale\$ or qtime\$.ti,ab,kf. 18055  
49 (illness state\$1 or health state\$1).ti,ab,kf. 9826  
50 (hui or hui1 or hui2 or hui3).ti,ab,kf. 2333  
51 (multiattribute\$ or multi attribute\$.ti,ab,kf. 1716  
52 (utility adj3 (score\$1 or valu\$ or health\$ or cost\$ or measur\$ or disease\$ or mean or gain  
or gains or index\$)).ti,ab,kf. 25042  
53 utilities.ti,ab,kf. 11077  
54 (eq-5d or eq5d or eq-5 or eq5 or euro qual or euroqual or euro qual5d or euroqual5d or  
euro qol or euroqol or euro qol5d or euroqol5d or euro quol or euroquol or euro quol5d or  
euroquol5d or eur qol or eurqol or eur qol5d or eur qol5d or eur?qul or eur?qul5d or euro\$  
quality of life or european qol).ti,ab,kf. 22760  
55 (euro\$ adj3 (5 d or 5d or 5 dimension\$ or 5dimension\$ or 5 domain\$ or  
5domain\$)).ti,ab,kf. 7702  
56 (sf36\$ or sf 36\$ or sf thirtysix or sf thirty six).ti,ab,kf. 30402  
57 (time trade off\$1 or time tradeoff\$1 or tto or timetradeoff\$1).ti,ab,kf. 2885  
58 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 116730  
**59 16 and 45 803 - economic evaluations**  
**60 16 and 58 118 - HRQoL studies**

**10. Additional information that is needed by NETSCC, HTA and NICE.**  
**Please send this as a WORD document when you submit your protocol to**  
[esptar@nihr.ac.uk](mailto:esptar@nihr.ac.uk)

**Details of EAG**

Matt Stevenson

Professor of Health Technology Assessment, Health Economics and Decision Science  
SCHARR, University of Sheffield

E-mail address: [REDACTED]

Munira Essat

Senior Research Fellow, Health Economics and Decision Science  
SchARR, University of Sheffield

[REDACTED]

[REDACTED]

Katy Cooper

Senior Research Fellow, Health Economics and Decision Science  
SchARR, University of Sheffield

[REDACTED]

Andrew Metry

Research Fellow, Health Economics and Decision Science  
SCHARR, University of Sheffield

[REDACTED]

Sarah Ren

Research Fellow, Health Economics and Decision Science  
SCHARR, University of Sheffield

[REDACTED]

Jen-Yu Amy Chang

Research Fellow, Health Economics and Decision Science  
SCHARR, University of Sheffield

X [REDACTED]

Yashwini Chandrawat  
Research Associate, Health Economics and Decision Science  
SCHARR, University of Sheffield



Mark Clowes  
Information Specialist, Health Economics and Decision Science  
ScHARR, University of Sheffield



Gill Rooney  
Programme Administrator  
SCHARR, University of Sheffield



***Please indicate to whom you wish all correspondence to be addressed***

Professor Matt Stevenson, copying in Gill Rooney.

## 11. References

1. Tan WK, Ross-Innes CS, Somerset T, et al. Biomarker risk stratification with capsule sponge in the surveillance of Barrett's oesophagus: prospective evaluation of UK real-world implementation. *Lancet* 2025;406:271-82. doi: [https://dx.doi.org/10.1016/S0140-6736\(25\)01021-9](https://dx.doi.org/10.1016/S0140-6736(25)01021-9)
2. National Institute for Health & Care Excellence (NICE). Gastro-oesophageal reflux disease and dyspepsia in adults: investigation and management: NICE,; 2019 [Available from: <https://www.nice.org.uk/guidance/cg184> accessed 22/09/2025 2025.
3. Fitzgerald RC, di Pietro M, Ragnath K, et al. British Society of Gastroenterology guidelines on the diagnosis and management of Barrett's oesophagus. *Gut* 2014;63(1):7-42. doi: 10.1136/gutjnl-2013-305372 [published Online First: 20131028]
4. National Institute for Health & Care Excellence (NICE). Barrett's oesophagus and stage 1 oesophageal adenocarcinoma: monitoring and management: NICE; 2023 [Available from: <https://www.nice.org.uk/guidance/ng231> accessed 22/09/2025 2025.
5. Centre for Reviews & Dissemination. Systematic Reviews: CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination, University of York, 2008. Available at: [https://www.york.ac.uk/media/crd/Systematic\\_Reviews.pdf](https://www.york.ac.uk/media/crd/Systematic_Reviews.pdf) [Last accessed: August 2021].
6. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 2009;339:b2700. doi: 10.1136/bmj.b2700
7. National Institute for Health & Care Excellence (NICE). NICE technology appraisal and highly specialised technologies guidance: the manual: NICE; 2025 [Available from: <https://www.nice.org.uk/process/pmg36> accessed 25/02/2026 2026.
8. Health Technology Wales. Capsule sponge devices to detect Barrett's oesophagus and early-stage oesophageal cancer: Health Technology Wales; 2025 [Available from: <https://healthtechnology.wales/reports-guidance/capsule-sponge-devices/> accessed 30/01/2026 2026.
9. Sterne JAC, Savovic J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;366:14898. doi: 10.1136/bmj.14898 [published Online First: 2019/08/30]
10. Tomlinson E, Yang B, Davenport CF, et al. Piloting QUADAS-3: a revised tool for the quality assessment of diagnostic accuracy studies. *Journal of Clinical Epidemiology* 2025;188:111983. doi: <https://doi.org/10.1016/j.jclinepi.2025.111983>
11. Derezea E, Ades AE, Rogers G, et al. Evidence synthesis of diagnostic test accuracy for decision making: Technical Support Document 25. 2024 2024 [Available from: <https://sheffield.ac.uk/nice-dsu> accessed 22/09/2025 2025.
12. Deeks J, Bossuyt P, Leeflang M, et al. Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy. In: John Wiley & Sons; 2023. *John Wiley & Sons*; 2023
13. rjags: Bayesian Graphical Models using MCMC [program], 2023.
14. Brooks SP, Gelman A. General Methods for Monitoring Convergence of Iterative Simulations. *Journal of Computational and Graphical Statistics* 1998;7(4):434-55. doi: 10.1080/10618600.1998.10474787
15. Arber M, Garcia S, Veale T, et al. Performance of Ovid MEDLINE search filters to identify health state utility studies. *Int J Technol Assess Health Care* 2017;33(4):472-80. doi: 10.1017/s0266462317000897 [published Online First: 2017/10/27]
16. NHS England. National schedule of NHS costs. 2023. (accessed 2023).
17. National Institute for Health & Care Excellence (NICE). British National Formulary (BNF) 2025 [Available from: <https://bnf.nice.org.uk/> accessed 23/09/2025 2025.
18. Department of Health & Social Care. Drugs and pharmaceutical electronic market information tool (eMIT): GOV.UK; 2025 [Available from: <https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit> accessed 24/09/2025 2025.