Diagnostic Assessment Report commissioned by the NIHR HTA Programme on behalf of the National Institute for Health and Care Excellence – Protocol

Title of project

A systematic review and economic evaluation of SeHCAT (Tauroselcholic [^{75}Selenium] acid) for the investigation of bile acid diarrhoea.

Name of External Assessment Group (EAG) and project lead

Kleijnen Systematic Reviews Ltd.

Project lead:
Marie Westwood
Kleijnen Systematic Reviews Ltd
[redacted]
Tel: [redacted]
Email: [redacted]

Second contact:
Nigel Armstrong
Kleijnen Systematic Reviews Ltd
[redacted]
Tel: [redacted]
Email: [redacted]

Health economics lead:
Isaac Corro Ramos
institute for Medical Technology Assessment (iMTA)
Erasmus University
[redacted]
Tel: [redacted]
Email: [redacted]

1 Plain English Summary

Bile acids are produced in the liver, secreted into the biliary system, stored in the gall-bladder and are released after meals. They are important for the digestion and absorption of fats in the small intestine. Usually over 95% of the bile acids are absorbed in the terminal ileum and are taken up by the liver and re-secreted. When larger amounts of bile acids enter the large intestine, they stimulate salt and water secretion and intestinal motility in the colon, which causes symptoms of chronic diarrhoea. This is called bile acid diarrhoea or bile acid malabsorption (BAM).

Symptoms of bile acid diarrhoea may include explosive, smelly or watery diarrhoea, urgency in going to the toilet, abdominal pain, swelling or bloating and faecal incontinence.

A SeHCAT scan is a diagnostic procedure, which may help to tell whether diarrhoea is being caused by problems with bile acid absorption. It involves swallowing a capsule containing a very slightly radioactive tracer and imaging with a special camera shortly after swallowing the capsule and after a week. This then shows what percentage of bile acid has been absorbed, and thus whether the patient has bile acid diarrhoea.

The purpose of this project is to assess the clinical benefits, risks and cost-effectiveness of [^{75}Se] tauroselcholic acid (SeHCAT), a bile acid analogue which is used, in people with chronic diarrhoea with an unknown cause, with suspected or diagnosed irritable bowel syndrome or functional diarrhoea, or with a diagnosis of Crohn's disease and no ileal resection, who have been referred to secondary care for investigation of possible bile acid diarrhoea.

2 Decision problem

2.1 Population

The primary indication for this assessment is the investigation of possible bile acid diarrhoea in adults presenting with chronic diarrhoea with an unknown cause, suspected or diagnosed diarrhoea predominant irritable bowel syndrome (IBS-D), or functional diarrhoea (i.e. people with suspected primary bile acid diarrhoea).

Bile acid diarrhoea is a form of chronic diarrhoea. In bile acid diarrhoea, the recycling of bile acids in the body is not functioning properly. Bile acids are produced by the liver and stored in the gallbladder until they are released into the small intestine to aid digestion. Usually, bile acids are reabsorbed into the liver in the final section of the small intestine. If they are not reabsorbed or the body produces more bile acid than can be reabsorbed, excess amounts of bile travels from the small bowel to the colon, stimulates salt and water secretion and bowel movements and results in diarrhoea.

Symptoms of bile acid diarrhoea may include explosive, smelly or watery diarrhoea, urgency in going to the toilet, abdominal pain, swelling or bloating and faecal incontinence.

The most common form of bile acid diarrhoea is caused by overproduction of bile acid in people with no physical damage to the bile acid recycling system. This primary form of bile acid diarrhoea is often missed as a cause of chronic diarrhoea. Because of the similarity in symptoms between bile acid diarrhoea and both IBS-D and functional diarrhoea, bile acid diarrhoea may be misdiagnosed. The actual cause of diarrhoea in up to a 30% of people with suspected IBS-D or functional diarrhoea may be bile acid diarrhoea.(1)

Bile acid diarrhoea can also appear as a secondary condition after the small bowel or another part of the bile acid recycling system has been damaged by disease, surgery, or other clinical interventions (e.g. pelvic radiotherapy or chemotherapy).

This assessment will also consider SeHCAT for the investigation of possible secondary bile acid diarrhoea in adults with chronic diarrhoea and a diagnosis of Crohn's disease, who have not undergone ileal resection.

2.2 Intervention technology

SeHCAT (tauroselcholic [75 selenium] acid) is a radiopharmaceutical capsule that is indicated for use in the investigation of bile acid malabsorption (BAM) and measurement of bile acid pool loss. It may also be used in assessing ileal function, in the investigation of Inflammatory Bowel Disease (IBD) and chronic diarrhoea and in the study of enterohepatic circulation (these uses are outside of the current scope). SeHCAT is manufactured by GE Healthcare Limited.

The SeHCAT test is used to measure how well the body absorbs bile acids. The radiopharmaceutical capsule contains 75 Selenium (a gamma-emitter) and a synthetic version of bile acid (tauroselcholic acid). When swallowed, SeHCAT is absorbed by the body like a natural bile acid. It can be detected in the body using a gamma camera.

A SeHCAT test involves two outpatient appointments in the nuclear medicine department of a hospital. During the first appointment, the patient swallows a SeHCAT capsule and then waits for up to three hours before a baseline scan is taken. A follow-up scan is taken on day seven, after the first appointment. It may be considered reasonable to stop any anti-diarrhoeal medication for the duration of the test as there is a possibility that this may interfere with the test result.

The result of the test is given as the proportion of SeHCAT remaining in the body after seven days. To calculate the result, the amount of radioactivity detected in the follow-up scan is divided by the amount of radioactivity detected in the baseline scan. Diagnosis of bile acid diarrhoea is usually made when 15% or less of SeHCAT remains in the body. SeHCAT results are on a continuous scale, and hence the threshold used for a positive result can vary, however, retention values above 20% are not usually considered indicative of bile acid diarrhoea (clinical opinion of specialist committee members). SeHCAT results are also sometimes used to grade the severity of bile acid diarrhoea:

- retention values from 10% to 15% indicate mild bile acid diarrhoea
- retention values from 5% to 10% indicate moderate bile acid diarrhoea
- retention values from 0% to 5% indicate severe bile acid diarrhoea

In current clinical practice, the cut-off for a positive SeHCAT result may vary; a 2016 survey of 38 centres in the UK found that more than 50% used their own criteria for defining a positive SeHCAT result.(2)

There is no paediatric dosage form or clinical experience of the use of SeHCAT in children and evaluation of the clinical and cost effectiveness of SeHCAT in children is outside the scope of this assessment.

2.3 Alternative technologies

There are no alternative technologies, which are currently in routine use in the NHS, England and Wales.

2.4 Care pathway

Diagnosis

The initial investigation of patients with chronic diarrhoea should involve history taking, an assessment of clinical symptoms and signs to exclude cancer, as indicated in NICE guideline NG12 “Suspected cancer: recognition and referral.”(3) The initial clinical assessment should

also include blood and stool tests to exclude anaemia, coeliac disease, infection and inflammation, as recommended in clinical guidelines: “Guidelines for the investigation of chronic diarrhoea in adults: British Society of Gastroenterology (BSG), 3rd edition.”(1) The BSG guidelines position SeHCAT testing as part of secondary clinical assessment, following initial assessment/investigations to exclude coeliac disease (coeliac serology and upper GI endoscopy and biopsy in people with suspected coeliac disease), common infections (stool examination for *C. difficile*, ova, cysts and parasites), and colorectal cancer (colonoscopy in people with altered bowel habit and rectal bleeding, and faecal immunochemical testing to guide priority investigations in people with lower gastrointestinal symptoms and no rectal bleeding).(1)

The BSG guidelines list bile acid diarrhoea amongst the “common disorders” to be investigated as part of secondary clinical assessment and state that a positive diagnosis of bile acid diarrhoea should be made using either SeHCAT testing or serum bile acid precursor 7-alpha-hydroxy-4-cholesten-3-one, depending on local availability.(1) The BSG guidelines also state that “there is insufficient evidence to recommend use of an empirical trial of treatment for bile acid diarrhoea rather than making a positive diagnosis.”(1) The possible future audit goals listed in the BSG guideline include: “All patients with persistent undiagnosed chronic diarrhoea should be investigated for bile acid diarrhoea with SeHCAT or serum 7-alpha-hydroxy-4-cholesten-3-one or faecal bile acid measurement where available.” .”(1) Referral to secondary care is required for investigation and diagnosis of bile acid diarrhoea.

NICE clinical guideline CG61 “Irritable bowel syndrome in adults: diagnosis and management” recommends considering a diagnosis of irritable bowel syndrome (IBS), in patients with abdominal pain or discomfort that is either relieved by defaecation or associated with altered bowel frequency or stool form, when the initial investigations are normal and at least two of the following symptoms are present: altered stool passage (straining, urgency, incomplete evacuation); abdominal bloating (more common in women than men), distension, tension or hardness; symptoms worsened by eating; passage of mucus.(4) The guideline also states that further tests such as colonoscopy or imaging are not necessary to confirm an IBS diagnosis.(4) Investigation of bile acid diarrhoea may be useful in patients previously diagnosed with IBS-D, however, NICE clinical guideline CG61 does not currently include any recommendations on the investigation of bile acid diarrhoea.(4)

Investigation of bile acid diarrhoea may also be considered when diarrhoea persists regardless of conventional treatment in those conditions where it may appear as a secondary condition. When chronic diarrhoea appears after ileal resection (removal of the terminal part of the small bowel to treat Crohn’s disease), bile acid diarrhoea is so common (more than 95% of cases) that a diagnostic test before treatment may not be considered necessary.

The use of SeHCAT in current clinical practice appears to vary, with some studies indicating that imaging tests and invasive investigations such as colonoscopy are often performed before SeHCAT.(2, 5, 6) Multiple interactions with different clinicians over many years often take place before bile acid diarrhoea is investigated.(7)

The manufacturer advises that SeHCAT testing is currently available at 85 hospitals across 74 of 225 NHS acute trusts in England (data from August 2020). According to the 2018-2019 NHS National Cost Collection data,(8) the trusts with SeHCAT testing perform about 10,000 SeHCAT tests per year. The number of tests performed in different trusts ranges widely from less than 50 tests per year to more than 500 tests per year.

Treatment

The symptoms of bile acid diarrhoea are most often controlled with bile acid sequestrant medication. Bile acid sequestrants bind to bile acids in the small bowel and prevent them from irritating the colon, and can also slow transit time. The treatment is often life-long.

There are currently three bile acid sequestrants available: colestyramine, colestipol and colesevelam. Colestyramine and colestipol come in powder or granule form and colesevelam in tablet form. Use of both colestipol and colesevelam for bile acid diarrhoea is currently off-label (NICE Evidence summary ESUOM22 "Bile acid malabsorption: colesevelam."(9) Bile acid sequestrants can be difficult to tolerate; constipation and flatulence are commonly reported adverse events, some people find the taste and texture of colestyramine and colestipol very unpleasant, and some patients have reported weight gain associated with thee treatments. Supplementation with vitamins A, D, E and K and folic acid may be required with long-term therapy.(10) Increases in dose, addition of anti-diarrhoea medication or changes in diet may also be needed to achieve adequate symptom control.

In current practice, in some Trusts, bile acid sequestrant treatment of bile acid diarrhoea is started without a diagnostic test being performed (trial of treatment). Trial of treatment may take between 4 and 12 weeks (clinical opinion of specialist committee members).

3 Objective

The overall objective of this project is to provide an update to NICE diagnostics guidance on SeHCAT (tauroselcholic [75 selenium] acid) for the investigation of diarrhoea due to bile acid malabsorption in people with diarrhoea-predominant irritable bowel syndrome (IBS-D) or Crohn's disease without ileal resection (DG7), published in November 2012. This update will summarise the current evidence on the clinical and cost effectiveness of [^{75}Se] tauroselcholic acid (SeHCAT) for investigating bile acid diarrhoea and the measurement of bile acid pool loss in adults referred to a secondary care for the investigation of chronic diarrhoea with an unknown cause, suspected or diagnosed diarrhoea predominant irritable bowel syndrome (IBS-D), or functional diarrhoea (i.e. people with suspected primary bile

acid diarrhoea). This up-date will also consider SeHCAT for the investigation of possible secondary bile acid diarrhoea in adults with chronic diarrhoea and a diagnosis of Crohn's disease, who have not undergone ileal resection.

In order to address this objective, the following research questions have been defined:

- What are the effects of a care pathway which includes a SeHCAT test compared to no SeHCAT test in terms of clinical symptoms, other relevant health outcomes and costs, in adults with chronic diarrhoea, in the specified populations?
- Does the result of a SeHCAT test predict response to treatment with bile acid sequestrants (BAS) in adults with chronic diarrhoea, in the specified populations?
- What is the cost effectiveness of including a SeHCAT test in the diagnostic care pathway for the investigation of chronic diarrhoea, in the specified populations?

4 Methods for assessing clinical effectiveness

A systematic review will be conducted to summarise the evidence on the clinical effectiveness of SeHCAT for the investigation and diagnosis of bile acid diarrhoea. Systematic review methods will follow the principles outlined in the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care,(11) NICE Diagnostics Assessment Programme manual(12) and the Cochrane Handbook for Diagnostic Test Accuracy Reviews.(13) All data for studies included in the original Diagnostic Assessment Report (DAR),(14) conducted to support the development of DG7,(15) will be taken directly from that report.

4.1 Inclusion and exclusion criteria

Participants

Study populations eligible for inclusion will be:

Adults (age ≥18 years) referred to a GI clinic for investigation and diagnosis of possible bile acid diarrhoea, who have previously undergone primary clinical assessment/investigations (as recommended in the BSG guidelines(1)) to exclude coeliac disease (coeliac serology and upper GI endoscopy and biopsy in people with suspected coeliac disease), common infections (stool examination for *C. difficile*, ova, cysts and parasites), and colorectal cancer (colonoscopy in people with altered bowel habit and rectal bleeding, and faecal immunochemical testing to guide priority investigations in people with lower gastrointestinal symptoms and no rectal bleeding). Given the paucity of evidence identified by our initial scoping searches, studies which do not fully report prior investigations, or where prior investigations do not match those specified above, will be included. The issue of mismatch between the available evidence and the specified population will be addressed in the quality assessment of included studies and synthesis of results, as necessary.

As detailed above, this assessment will focus on two specific populations:

- Adults presenting with chronic diarrhoea with unknown cause, suspected or diagnosed IBS-D or functional diarrhoea (i.e. people with suspected primary bile acid diarrhoea)

- Adults presenting with chronic diarrhoea and a diagnosis of Crohn's disease, who have not undergone ileal resection (i.e. people with suspected secondary bile acid diarrhoea)

Setting
Secondary care.

Intervention (index test)
SeHCAT (Tauroselcholic [^{75}Selenium] acid) test, (GE Healthcare Limited, UK).

Comparators
For the purposes of cost effectiveness modelling, the comparators used in this assessment will be:

- No SeHCAT testing and no treatment with bile acid sequestrants
- No SeHCAT testing and trial of treatment with bile acid sequestrants

Outcomes
The following outcomes will be considered:

- Effect of testing on treatment plan (e.g. surgical or medical management, or further testing)
- Effect of testing on clinical outcome, (e.g. morbidity and adverse events)
- Effect of testing on adherence to treatment
- Prognosis - the ability of test result to predict clinical outcome (i.e. response to treatment)
- Predictive accuracy - sensitivity and specificity of SeHCAT for the prediction of treatment response

For included studies reporting any of the above outcome measures, the following outcomes will also be considered if reported:

- Acceptability of tests to patients or surrogate measures of acceptability (e.g. waiting time and associated anxiety).
- Adverse events associated with testing (e.g. pain/discomfort experienced during the procedure and waiting times before results).
- Health-related quality of life

Study design
The following types of studies will be included:

- Randomised or non-randomised controlled trials, or observational comparative studies where clinical or treatment planning outcomes are compared in patients who received SeHCAT testing vs. those who did not.
    - Observational comparative studies will only be included if no randomised or non-randomised controlled trials are identified.
- Randomised or non-randomised controlled trials, or observational comparative studies, where all patients receive SeHCAT testing and clinical outcomes between treatment decisions based on different definitions of a positive SeHCAT result (different diagnostic thresholds).
    - Observational comparative studies will only be included if no randomised or non-randomised controlled trials are identified.
- Observational studies, where all patients received SeHCAT testing, and clinical or treatment planning outcomes are compared in patients with positive SeHCAT results vs. those with negative SeHCAT results.
- Observational studies which report the results of multi-variable regression modelling with response to treatment with bile acid sequestrants as the dependent variable and index test result (continuous or categorical) as an independent variable. Included studies should control adequately for potential confounders (e.g. age, gender, comorbidities, etc.). Studies using any reported threshold for a positive SeHCAT test and any reported definition of response to treatment will be included.
- Predictive accuracy studies, which report sufficient data to support the calculation of the sensitivity and specificity of SeHCAT to predict response to treatment with bile acid sequestrants (i.e. studies which report the outcome of treatment with bile acid sequestrants for both patients with a positive SeHCAT test and those with a negative SeHCAT test). Studies using any reported threshold for a positive SeHCAT test and any reported definition of response to treatment will be included.
    - Studies which report treatment outcome only for those participants with a positive SeHCAT result (i.e. sufficient data to calculate positive predictive value only) will only be included if no studies with full outcome data (for both SeHCAT positive and SeHCAT negative participants) are identified.

The following study/publication types will be excluded:

- Pre-clinical and animal
- Reviews, editorials, and opinion pieces
- Case reports
- Studies reporting only technical aspects of the test, or image quality
- Studies with <10 participants

4.2 Search strategy

Search strategies utilised in the original report will be updated in line with the NICE final Scope. Search strategies will be based on target condition and intervention, as

recommended in the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care and the Cochrane Handbook for Diagnostic Test Accuracy Reviews.(11, 13, 16)

Search strategies will be developed specifically for each database and the keywords associated with bile acid diarrhoea will be adapted according to the configuration of each database.

Additional supplementary searches will be carried out as necessary. Searches for studies for cost and quality of life will also be included, see Section 5 for further details.

The following databases will be searched for relevant studies from inception to the present (please note that this list has been amended from our previous systematic review(15) to account for changes in database availability):

- MEDLINE (Ovid)
- MEDLINE In-Process Citations, Daily Update and Epub Ahead of Print (Ovid)
- EMBASE (Ovid)
- Cochrane Database of Systematic Reviews (CDSR) (Wiley)
- Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley)
- Database of Abstracts of Reviews of Effects (DARE) (CRD)
- Health Technology Assessment Database (HTA) (CRD)
- Science Citation Index (SCI) (Web of Science)
- KSR Evidence
- LILACS (Latin American and Caribbean Health Sciences Literature) (Internet) http://regional.bvsalud.org/php/index.php?lang=en
- NIHR Health Technology Assessment Programme (Internet)
- PROSPERO (International Prospective Register of Systematic Reviews) (Internet) http://www.crd.york.ac.uk/prospero/

Completed and ongoing trials will be identified by searches of the following resources:

- NIH ClinicalTrials.gov (http://www.clinicaltrials.gov/)
- WHO International Clinical Trials Registry Platform (ICTRP) (http://www.who.int/ictrp/en/)

Key conference proceedings, to be identified in consultation with clinical experts, once agreed conferences will be checked against Embase and Northern Light Life Sciences Conference Abstracts to determine which proceedings are indexed within the databases. Where resources are not indexed in these databases, the proceedings will be searched manually for the last five years.

Identified references will be downloaded in Endnote X8 software for further assessment and handling.

References in retrieved articles and relevant systematic reviews will be checked.

The main Embase search strategy for each set of searches will be independently peer reviewed by a second Information Specialist, using the PRESS-EBC checklist.(17)

No restrictions on language or publication status will be applied. Limits will be applied to remove animal studies. Searches will take into account generic and other product names for the intervention. Examples of the search strategies to be used are presented in Appendix 1.

4.3 Review methods

Two reviewers will independently screen titles and abstracts of all reports identified by searches and discrepancies will be discussed. Full copies of all studies deemed potentially relevant, after discussion, will be obtained and two reviewers will independently assess these for inclusion; any disagreements will be resolved by consensus or discussion with a third reviewer.

Where available/applicable, data will be extracted on the following: study design/details, participant characteristics (e.g. demographic characteristics, comorbidities, symptom duration/severity, previous investigations), details of the application of the SeHCAT test (e.g. threshold used to define a positive test result), details of any treatments received for bile acid diarrhoea (e.g. bile acid sequestrant used and dosing regimen, and any concomitant treatments such as diet or loperamide), and the definition of response to treatment including duration of follow-up, outcomes (as defined in section 4.1). Data will be extracted by one reviewer, using data extraction forms based on those used for the original systematic review(14) conducted to support the development of DG7.(15) A second reviewer will check data extraction and any disagreements will be resolved by consensus or discussion with a third reviewer.

4.4 Quality assessment

The methodological quality of included RCTs will be assessed using the revised Cochrane Risk of Bias Tool for Randomised Trials (RoB 2).(18) Diagnostic accuracy studies will be assessed using QUADAS-2.(19) Appropriate methodological quality assessment tools will be selected for observational comparative studies, according to the study designs identified. The results of the quality assessment will be used for descriptive purposes to provide an evaluation of the overall quality of the included studies and to provide a transparent method of recommendation for design of any future studies. Where sufficient data are available the results of quality assessment may be used to inform stratified meta-analyses in order to explore the impact if individual components of study quality upon the findings of the review. Quality assessment will be undertaken by one reviewer and checked by a second reviewer, any disagreements will be resolved by consensus or discussion with a third reviewer.

4.5 Data synthesis

If available data allow, summary estimates of the sensitivity and specificity together with 95% confidence intervals (CIs) and prediction regions of SeHCAT will be calculated. Analyses will be conducted separately for each different diagnostic threshold (definition of a positive index test result), definition of treatment response (definition of a positive reference standard), and clinical population, for which sufficient data are available. We will use the bivariate/hierarchical summary receiver operating characteristic (HSROC) random effects model to generate summary estimates and an SROC curve.(20-22) If more than one RCT evaluates the same outcome in the same clinical population, using the same intervention and comparator, then data will be pooled on treatment effect (e.g. hazard ratio, odds ratio, relative risk, weighted mean difference). The DerSimonian and Laird random effects model will be used to generate summary estimates together with 95% CIs.

Where meta-analysis is considered unsuitable for some or all of the data identified (e.g. due to the heterogeneity and/or small numbers of studies), we will employ a narrative synthesis. Typically, this will involve the use of text and tables to summarise data. These will allow the reader to consider any outcomes in the light of differences in study designs and potential sources of bias for each of the studies being reviewed.

The report will be structured by clinical application (diagnosis of primary bile acid diarrhoea and diagnosis of secondary bile acid diarrhoea in people with Crohn's disease who have not undergone ileal resection. A detailed commentary on the major methodological problems or biases that affected the studies will also be included, together with a description of how this may have affected the individual study results. Recommendations for further research will be made based on any gaps in the evidence or methodological flaws.

5 Methods for synthesising evidence of cost effectiveness

5.1 Identifying and reviewing published cost effectiveness studies

Exploration of the literature regarding published economic evaluations, utility studies and cost studies will be performed in relevant literature databases listed above. In addition, specific health economic databases will be searched (e.g. NHSEED (NHS Economic Evaluation Database), Research Papers in Economics (REPEC), CEA Registry and ScHARRHUD (Internet). Searches will focus on original papers that report on cost, cost-accuracy, cost-effectiveness or cost-utility analyses, either studying the diagnostic phase (test performance in terms of detecting bile acid diarrhoea in the populations of interest), therapeutic phase (patients with bile acid diarrhoea), or a combination. For our assessment cost studies, utility studies and full economic evaluations, i.e. those that explicitly compare different decision options will be selected. Clinical trials as well as modelling studies and cohort studies will be relevant within the frame of our project. The intention is not to perform a systematic review, but to use the studies identified to support the development of an economic model

and estimation of model input parameters that will aim to answer the research questions of this project.

The results and the methodological quality of the studies selected will be summarised. Data extraction will focus on technologies compared, indicated population, main results in terms of costs and consequences of the alternatives compared, and the incremental cost-effectiveness, but also on methods of modelling used (if applicable), analytical methods and robustness of the study findings.

Targeted searches for input parameters in the economic model will be performed if deemed necessary (on an ad-hoc basis).

5.2 Evaluation of costs, quality of life and cost effectiveness

The cost-effectiveness of SeHCAT for the assessment of bile acid diarrhoea, will be estimated in two different patient populations (see section 2.1 for further details):

- Adults with chronic diarrhoea with an unknown cause, suspected or diagnosed diarrhoea predominant irritable bowel syndrome (IBS-D), or functional diarrhoea (i.e. people with suspected primary bile acid diarrhoea). The condition in this population is referred to as primary bile acid diarrhoea.
- Adults with chronic diarrhoea and a diagnosis of Crohn's disease, who have not undergone ileal resection. The condition in this population is referred to as secondary bile acid diarrhoea.

Therefore, two separate economic models, one for each population, will be developed, analysed, and their results will be reported independently. If data allows it, all models will evaluate the cost effectiveness of SeHCAT compared to:

- No SeHCAT testing and no treatment with bile acid sequestrants,
- No SeHCAT testing and trial of treatment with bile acid sequestrants.

All costs and effects will be discounted by 3.5%. The model will incorporate a lifetime time horizon to estimate outcomes in terms of quality-adjusted life years (QALYs) and costs from the perspective of the NHS. Only health effects of patients will be included.

For the SeHCAT treatment option (and for all populations) various strategies will be defined, based on the test cut-off points used (see section 2.2 for additional details), to classify patients. According to the clinical experts at the scoping meeting, these test cut-off points may vary for different patient populations and between institutions. Thus, final cut-off points will be selected depending on data availability. In the previous assessment of SeHCAT, cut-off points of 5%, 10% and 15% were used.(14)

Where possible, input for the model will be based on our SeHCAT systematic review (described in section 4), other published literature and UK databases. When such evidence was not available, expert opinion will be used.

Model structure

The proposed conceptual models will be in line with those used in the previous assessment of SeHCAT.(14) Final model structures may change from those presented in the remaining of this section following consultation with clinical experts.

For each population, two models will be combined:

- a short-term decision tree that models the diagnostic pathway and initial response to treatment (first six months), and
- a long-term (Markov) model that estimates the lifetime costs and effects for patients receiving subsequent treatment.

Parameter uncertainty will be explored through probabilistic sensitivity analyses and structural uncertainty through scenario analyses. Final outcomes will be expressed as additional cost per additional quality adjusted life year.

An outline of the proposed models for the first population (adults with suspected primary bile acid diarrhoea) is presented in Figure 1. In the SeHCAT strategy, patients may have a positive or negative test result. If the test is positive, i.e. the percentage of absorbed bile acids is below a certain cut-off point, patients are treated with BAS and they may or may not respond to that treatment. Patients with a positive SeHCAT result and an initial response to BAS are at risk of treatment discontinuation due to BAS intolerance (or adverse events). In this case, patients do not go through further testing, because, given the positive SeHCAT result, it is assumed that these patients will be treated as having BAD but an alternative to BAS should be provided. If the test is negative, a proportion of patients will be investigated for IBD with a colonoscopy, unless clinical experts suggest otherwise. If after the colonoscopy, patients are diagnosed as IBD, then they will be treated accordingly. Otherwise, patients will be treated as having IBS-D. Patients testing SeHCAT negative and not undergoing colonoscopy will also be diagnosed as IBS-D and be treated accordingly. All endpoints of the SeHCAT negative branch, will be determined depending on whether patients respond to treatment or not. The first no SeHCAT strategy assumes that all patients follow the same paths as in the SeHCAT negative test. Thus, patients may be investigated for IBD with a colonoscopy, may be treated for IBD or IBS-D and may or may not respond to treatment. Finally, in the trial of treatment strategies, all patients receive BAS. If patients do not respond to this, they follow the same paths as in the SeHCAT negative test and the no SeHCAT strategies. Patients with an initial response to BAS are also at risk of treatment discontinuation due to BAS intolerance (or adverse events), as in the SeHCAT positive

branch of the model. Note that treatment discontinuation may vary between patients with a positive SeHCAT result and those not tested. This distinction may be included provided that data are available.

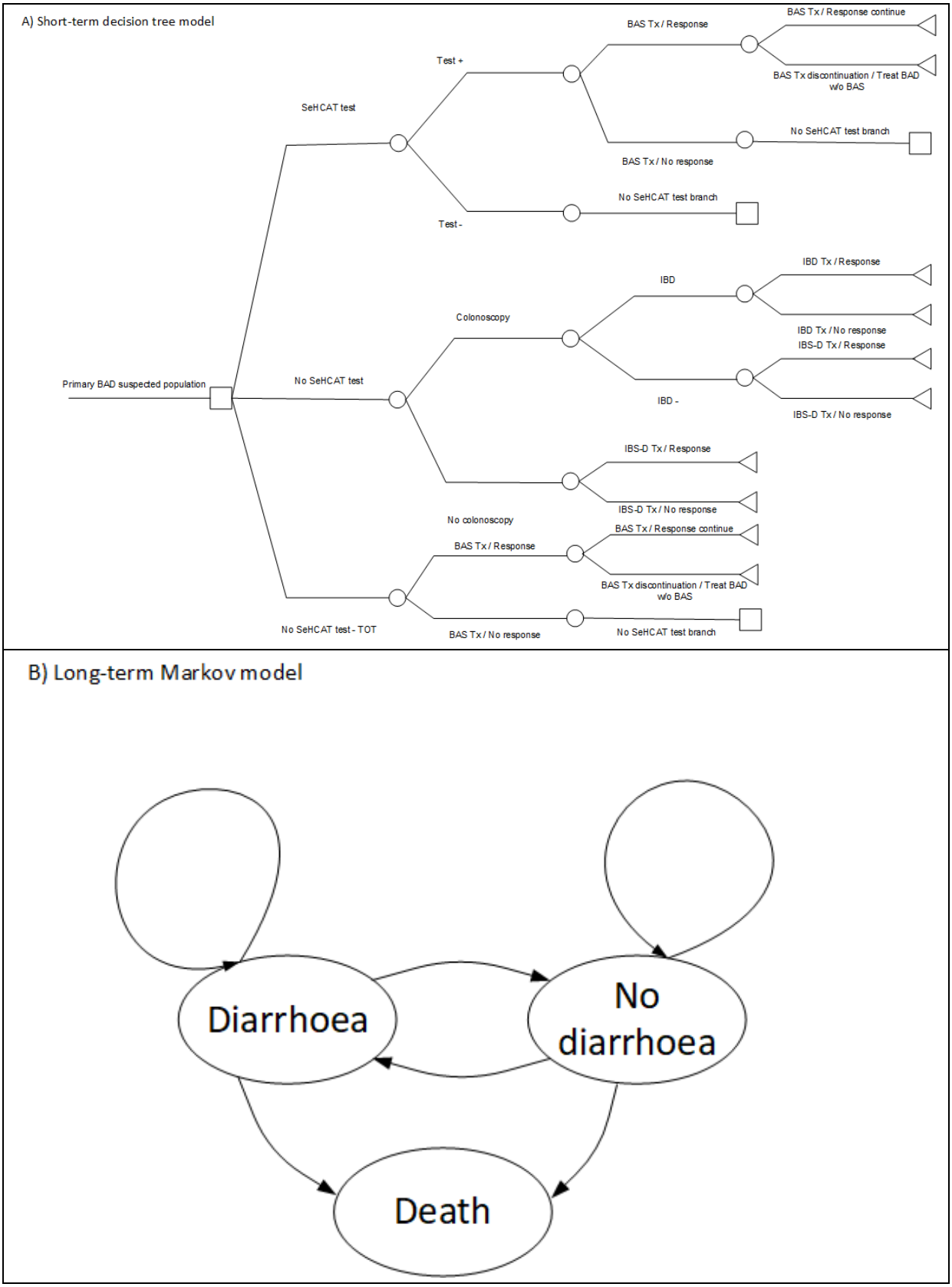
The main difference with the previous assessment of SeHCAT,(14) is the inclusion of the colonoscopy investigation in the model. This was based on clinical experts suggesting that SeHCAT could be used to avoid unnecessary colonoscopies.

To assess the long-term costs and effects of the various strategies, patients will be assumed to enter a three-state Markov model (see Figure 1B). Patients who had a treatment response start in the “no diarrhoea” health state and patients who did not respond to treatment start in the “diarrhoea” state. As the model has a lifetime time horizon, the third state included is death. In the previous assessment of SeHCAT, no link with increased mortality was found.(14) Therefore, unless there is new evidence to suggest that this has changed, only background mortality will be considered in the economic model. Patients are allowed to move between the “no diarrhoea” and the “diarrhoea” health states from one cycle to another, stay in the same health state or die. Transitions between the “diarrhoea” and “no diarrhoea” health states should be informed by clinical data regarding the long-term effectiveness (i.e. whether patients respond to treatment or not) of BAS, IBD and IBS-D treatments. These treatments may include diet adjustments/cost of nutritionist as in the previous assessment of SeHCAT.(14) Should these data not be available, clinical expert opinion or modelling assumptions will be used to inform these transitions. A simplified long-term model (e.g. an overall BAD state rather than cycling between diarrhoea and no diarrhoea) might be explored, if such simplifications are deemed realistic by clinical experts. This could be implemented in the 3-state model by setting some transitions to 0 (so that it may become a 2-state model). As mentioned above, the final model structure may be changed after consultation with experts. The cycle length used in the previous assessment of SeHCAT was six months.(14) This was estimated based on the responses of the clinical experts to the questionnaire included in the previous SeHCAT report (Appendix 9). Experts provided several ranges with a minimum value of 3 months, and a maximum of more than a year. Unless new evidence suggests otherwise, the same cycle length of six months will be considered here. If data allows it, adverse events, such as constipation, and treatment discontinuation will be included in the Markov model.

The proposed short-term model for the second population (adults with chronic diarrhoea and a diagnosis of Crohn’s disease, who have not undergone ileal resection) is shown in Figure 2. The main difference with respect to the short-term model in Figure 1A is that colonoscopy is not expected to be undergone in Crohn's patients with a negative SeHCAT or no SeHCAT test, since it is assumed that these patients would already have had colonoscopy to diagnose the Crohn's disease. Therefore, all endpoints of the decision tree model will be determined depending on whether patients respond to treatment (BAS- or Crohn’s-related

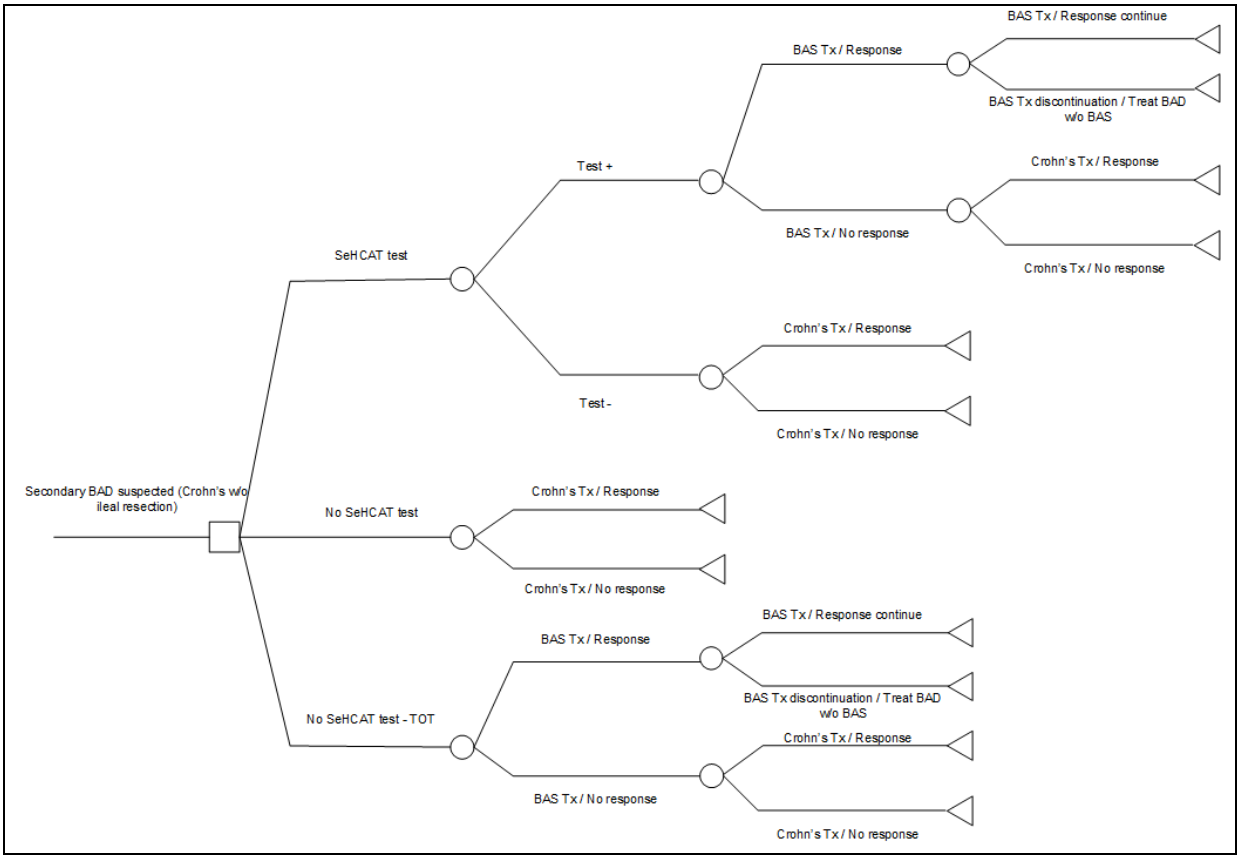
treatments) or not. This is the same structure assumed in the previous assessment of SeHCAT.(14) The long-term costs and effects of the various strategies will be assessed by a Markov model with the same structure as shown in Figure 1B.

Figure 1. Schematic representation of the proposed cost effectiveness models for the population of adults with suspected primary bile acid diarrhoea



Abbreviations: BAD = bile acid diarrhoea, BAS = bile acid sequestrants, IBD = inflammatory bowel disease, IBS-D = irritable bowel syndrome diarrhoea, TOT = trial of treatment, Tx = treatment

Figure 2. Schematic representation of the proposed short-term cost effectiveness model for the population of adults with suspected secondary bile acid diarrhoea (Crohn's disease without ileal resection)



Abbreviations: BAD = bile acid diarrhoea, BAS = bile acid sequestrants, TOT = trial of treatment, Tx = treatment, w/o = without

Health outcomes

Utility values, based on literature or other sources, will be incorporated in the economic model for the various health states. QALYs will be calculated from the economic modelling. Additionally, short-term consequences may also be expressed as the proportion of patient response to treatment, as in the previous assessment of SeHCAT,(14) or as the number of colonoscopies avoided. Based on evidence availability and the feasibility of the cost-effectiveness model structure, other health outcomes may be analysed, as well.

Resource use and costs

Resource utilisation will be estimated for the costs of a SeHCAT test, the cost of a colonoscopy, and the costs of treatment of BAD, IBD, IBS-D and the cost of treatment of diarrhoea in Crohn's patients. Data for the cost analyses will be drawn from routine NHS sources (e.g. NHS reference costs, Personal Social Services Research Unit (PSSRU), British National Formulary (BNF)) and discussions with individual hospitals.

6 Handling of information from the companies

All data submitted by the manufacturers/sponsors will be considered if received by the EAG no later than 19/02/2021. Data arriving after this date will 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 'commercial in confidence' data provided by manufacturers, and specified as such, will be highlighted in blue and underlined in the assessment report (followed by company name in parentheses). Any 'academic in confidence' data provided by manufacturers, and specified as such, will be highlighted in yellow and underlined in the assessment report. Any confidential data used in the cost-effectiveness models will also be highlighted.

7 Competing interests of authors

None

8 Timetable/milestones

Milestones	**Completion data**
Draft protocol	28/10/2020
Final protocol	20/11/2020
Progress report	19/02/2021
Draft assessment report	19/04/2021
Final assessment report	18/05/2021

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Appendix 1: Clinical effectiveness search

Embase (Ovid): 1974-2020/11/10
Search Strategy: CN_SeHCAT2020_Emb2
Searched 11.11.20

(SeHCAT OR BAS) + BAM (No A)

1 tauroselcholic acid/ (234)
2 (tauroselcholic or selenohomocholyltaurine or 75018-71-2).ti,ab,ot,hw,rn,tn. (397)
3 (SeHCAT or Se-HCAT or 75SeHCAT or Se-75 or 75-SeHCAT or SE75).ti,ab,ot,hw,tn. (1591)
4 (23-seleno-25-homo-tauro-cholic acid or selenium homocholic acid taurine or 23-selena-25-homocholyltaurine or 23-selena-25-homotaurocholate or 23- selena-25-homotaurocholic-acid or selenium radioisotopes or tauroselenocholic acid or 75Se-homotaurocholate).ti,ab,ot,hw,tn. (52)
5 (selenium adj3 "75").ti,ab,ot,hw,tn. (857)
6 or/1-5 (2172)
7 bile acid sequestrant/ (1458)
8 ((bile adj3 (acid or salt) adj3 sequest$) or BAS).ti,ab,ot,hw,rn. (19030)
9 Colestipol/ or (Colestipol or cholestabyl or cholestipol or colestid or diethylenetriamine-epichlorohydrin-copolymer or diethylenetriamine-polymer-with-1-chloro-2,3-epoxypropane or epichlorohydrin-copolymer-with-diethylenetriamine or flavored-colestid or lestid or u-26,597a or u-26597-a or u-26597a or u-26,597a or 25085-17-0 or 37296-80-3 or 50925-79-6).ti,ab,ot,hw,rn,tn. (2934)
10 Colestyramine/ or (colestyramine or chol-less or choles or cholesthexal or cholestyramin or cholestyramine or cholybar or cholytar or colestepril or colestiramina or colestran or colestrol or colestyramin or cuemid or lipocol-merz or lismol or locholest or prevalite or quantalan or questran or resincoles-tiramina or resincolestiramina or vasosan-p-granulat or vasosan-s-granulat or 11041-12-6 or 58391-37-0).ti,ab,ot,hw,rn,tn. (11324)
11 Colesevelam/ or (Colesevelam or cholestagel or gt-31-104 or gt-31-104hb or gt-31-104 or gt-31-104hb or gt31-104 or gt31-104hb or gt31-104 or gt31-104hb or welchol or lodalis or 182815-43-6 or 182815-44-7).ti,ab,ot,hw,rn,tn. (1399)
12 aluminum hydroxide/ or (aluminum hydroxide or Ageldrate or al u creme or alcid or aldrox or algeldraat or algeldrate or algelox or alhydrogel or alkagel or alocol or alokreem or alterna gel or alu cap or alu-cap or alu-tab or alucol or aludrox or alugelibys or alumigel or alumina gel or alumina trihydrate or aluminium hydroxide or aluminium hydroxyde or aluminoid or aluminox or aluminum hydrate or aluminum hydroxide gel or aluminum oxide trihydrate or aluminum trihydrate or alutab or amphogel or amphojel or amphotabs or antiphos or bayerite or chefarox or collumina or collumol or colodral or colugel or creamalin or cremorin or diplogel or f 1000 or f1000 or fluagel or gastracol or gastrosetarderm or gelumina or hoemigel or hycolal or hydracoll or hydrated alumina or hydrolum or hydronal or hydroxal or lactalumina or neutroxide or palliacol or pepsamar or ulcerin-p or vanogel or 21645-51-2 or 1330-44-5 or 80206-84-4 or brasivil or rocgel or alugel or hydrated alumina or basalgel or dialume or nephrox).ti,ab,ot,hw,rn,tn. (10865)
13 or/7-12 (41706)
14 6 or 13 (43680)
15 (BAM or I-BAM or IBAM or PBAM or BSM).ti,ab,ot,hw. (5086)
16 primary bile acid diarrh?ea$.ti,ab,ot,hw. (38)
17 chronic diarrhea/ or bile acid/ or bile salt/ (36156)
18 ((chronic or explosive or smelly or watery or recur$ or persist$ or protract$ or continual$ or continuous$ or sustain$ or constant$ or relentless$ or unrelent$ or functional or aggressive) adj2 (diarrh?e$ or diarrea$ or f?eces)).ti,ab,ot,hw. (16671)
19 (malabsorb$ or mal-absorb$ or malabsorp$ or mal-absorp$).ti,ab,ot,hw. (23929)

20 ((bile or biliary) adj3 (acid$ or salt$)).ti,ab,ot,hw. (50021)
21 or/15-20 (92094)
22 14 and 21 (5763)
23 animal/ (1488294)
24 animal experiment/ (2614973)
25 (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).mp. (6891676)
26 or/23-25 (6891676)
27 exp human/ (21668053)
28 human experiment/ (525707)
29 or/27-28 (21669822)
30 26 not (26 and 29) (5273912)
31 22 not 30 (4716)