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

1. Title of project

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

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

Kleijnen Systematic Reviews Ltd.

Project lead:
Rob Riemsma
Kleijnen Systematic Reviews Ltd
Unit 6, Escrick Business Park
Riccall Road
Escrick
York YO19 6FD
Tel: 01904 727986
Email: rob@systematic-reviews.com

Second contact:
Jos Kleijnen
Kleijnen Systematic Reviews Ltd
Unit 6, Escrick Business Park
Riccall Road
Escrick
York YO19 6FD
Tel: 01904 727981
Email: jos@systematic-reviews.com

Health economics lead:
Maiwenn Al
institute for Medical Technology Assessment (iMTA)
Erasmus University
P.O. Box 1738
3000 DR Rotterdam
The Netherlands
Tel: +31-10-4088565
Email: al@bmg.eur.nl

3. 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 resecreted. When larger amounts of bile acids enter the large intestine, they stimulate water secretion and intestinal motility in the colon, which causes symptoms of chronic diarrhoea. This is called bile acid malabsorption (BAM).

A SeHCAT scan is a diagnostic procedure, which looks at the function of the bowel. 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 which percentage of bile acid was absorbed, and thus whether the patient has BAM.

The purpose of this project is to assess the benefits, risks and cost-effectiveness of [^{75}Se] tauroselcholic acid (SeHCAT), a bile acid analogue which is used as a test for investigating bile acid malabsorption (BAM) and the measurement of bile acid pool loss in patients with chronic diarrhoea referred to a GI clinic for investigation and diagnosis of BAM. Patients with Crohn's disease with chronic diarrhoea will be assessed separately.

4. Decision problem

4.1. Objectives

The objective of this project is to evaluate the clinical and cost effectiveness of [^{75}Se] tauroselcholic acid (SeHCAT), a bile acid analogue which is used as a test for investigating bile acid malabsorption (BAM) and the measurement of bile acid pool loss in patients referred to a GI clinic for investigation and diagnosis of BAM.

This can be translated in the following research questions. For people with chronic diarrhoea with unknown cause and in people with Crohn's disease and chronic diarrhoea with unknown cause (i.e. before resection):

1. What are the effects of SeHCAT compared to no SeHCAT in terms of chronic diarrhoea, other health outcomes and costs?
2. What are the effects of bile acid sequestrants (BAS) compared to no BAS in people with a positive or negative SeHCAT test?
3. Does a positive or negative SeHCAT test predict improvement in terms of chronic diarrhoea, other health outcomes and costs?

4.2. Intervention technologies

For questions 1 and 3, SeHCAT is the intervention.

SeHCAT (GE Healthcare) is a radiopharmaceutical that is licensed 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.

SeHCAT product information lists its applications as:

Tauroselcholic acid is a bile acid analogue which shows identical physiological behaviour with naturally occurring bile acid conjugates. Following oral administration in normal subjects, approximately 95% of the labelled bile acid is absorbed, mainly by the terminal ileum during each enterohepatic cycle. The distribution of activity is almost entirely confined to the lumen of the biliary ducts, gut and liver. Whole body retention data from normal subjects showed 97 to 100% of [^{75}Se]tauroselcholic was excreted with a biological half-life of 2.6 days and that, in most cases, a small component of about 3% was eliminated with a mean half time of 62 days.[1]

For question 2 bile acid sequestrants are the relevant interventions. There are currently three bile acid sequestrants available: colestyramine, colestipol, and colesevelam. Where evidence is available, the effectiveness of fat restrictions and other dietary modifications will also be assessed.

4.3. Population

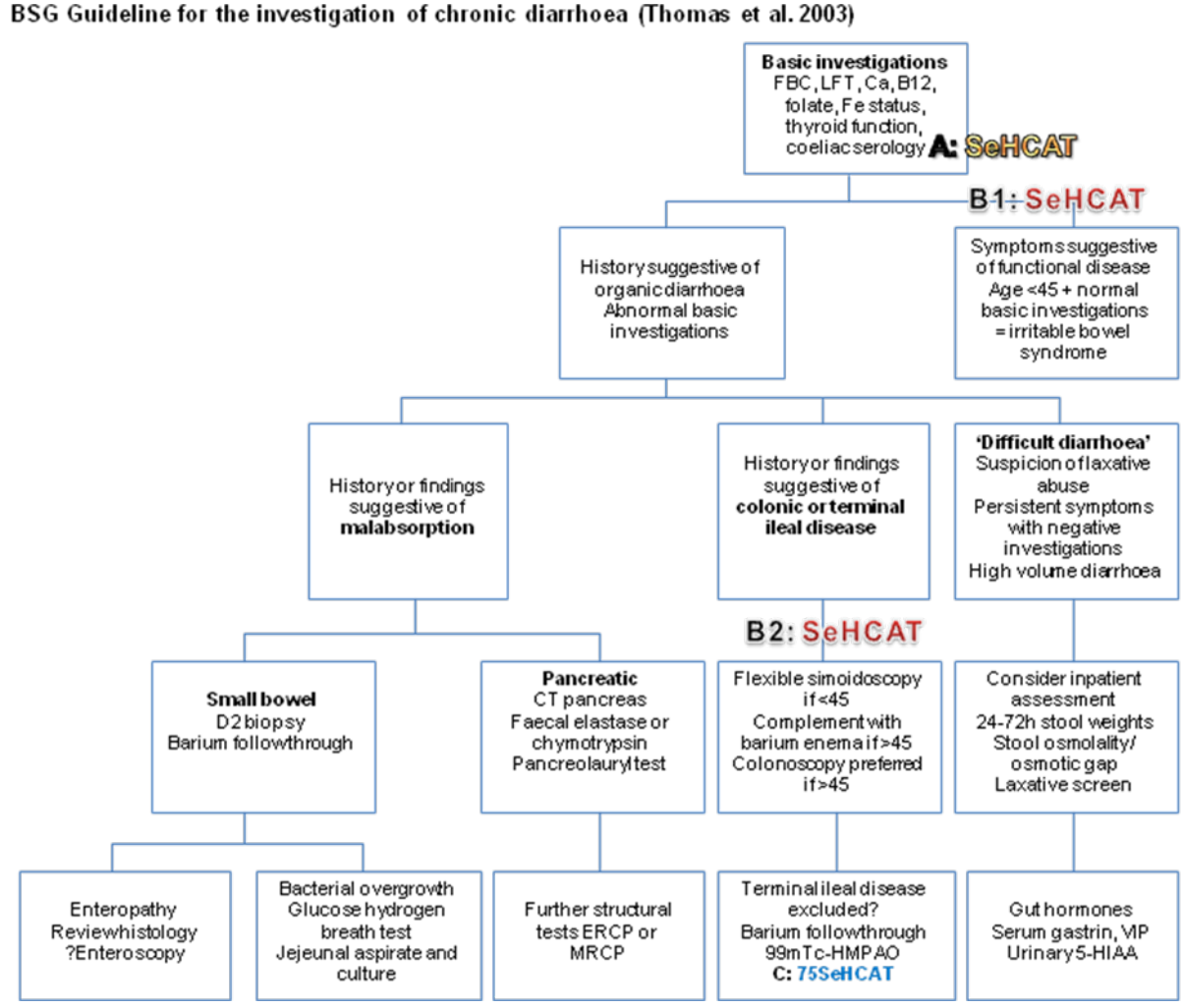
The populations for this evaluation are:

1. People presenting with chronic diarrhoea with unknown cause;
2. People with Crohn's disease and chronic diarrhoea with unknown cause (i.e. before resection of the terminal ileum)

4.4. Relevant comparators

There is no direct comparator for this diagnostic test. Current diagnostic options include analysis of a patient's history, investigations to exclude 'red flag' symptoms and a variety of other diagnostic tests such as blood tests and lactose tolerance tests. Trial of treatment and measurement of faecal bile acids are two methods used, with mixed results, to diagnose BAM. They are however, not widely used in current practice.

Figure 1: BSG diagnostic algorithm for chronic diarrhoea[2]



The current BSG guideline for chronic diarrhoea places SeHCAT at the end of the diagnostic algorithm (position C in Figure 1). Possible alternatives are:

1. SeHCAT as part of the basic investigations for all patients presenting with chronic diarrhoea (position A in Figure 1);
2. SeHCAT for all patients presenting with chronic diarrhoea and symptoms suggestive of functional disease (i.e. age < 45 and normal basic investigations) (position B1 in Figure 1); and also for patients with a history of findings suggestive of colonic or terminal ileal disease (position B2 in Figure 1).

SeHCAT as part of the basic investigations (position A in Figure 1), means that all patients presenting with chronic diarrhoea will be tested with SeHCAT. However, during the scoping workshop clinical experts advised that a positive SeHCAT test at this stage does not rule out the possibility of organic disease. As no subsequent tests for organic disease are made redundant, it is unlikely that SeHCAT in position A will be more cost-effective than in position B1. Therefore, this protocol will focus on position B1.

The same applies to SeHCAT in position B2. A positive SeHCAT test in position B2 will most likely not stop clinicians from doing subsequent tests (e.g. simoisdoscopy, barium enema or colonoscopy). Therefore, position B2 will be treated the same as position C in this report.

This leaves two possible populations for investigation:

1. People presenting with chronic diarrhoea with unknown cause and symptoms suggestive of functional disease;
2. People with Crohn's disease and chronic diarrhoea with unknown cause (i.e. before resection of the terminal ileum)

For both populations, the intervention will be SeHCAT followed by the appropriate treatment (see figures 2 and 3); and the comparator will be appropriate treatment without SeHCAT.

5. Report methods for assessing clinical effectiveness

A systematic review will be conducted to summarise the evidence on the clinical effectiveness of SeHCAT for the assessment of bile acid malabsorption (BAM) and the measurement of bile acid pool loss. Systematic review methods will follow the principles outlined in the Centre for Reviews and Dissemination (CRD) guidance for undertaking reviews in health care[3] and NICE Diagnostic Assessment Programme interim methods statement.[4]

5.1. Inclusion and exclusion criteria

Participants

Study populations eligible for inclusion will be:

All patients (including children) referred to a GI clinic for investigation and diagnosis of BAM which is a common underlying cause of chronic diarrhoea and the measurement of bile acid pool loss.[5, 6]

As explained above, this report will focus on two specific populations:

1. People presenting with chronic diarrhoea with unknown cause and symptoms suggestive of functional disease;
2. People with Crohn's disease and chronic diarrhoea with unknown cause (i.e. before resection of the terminal ileum).

Setting

Relevant settings are primary or secondary care.

Interventions (index test(s))

For population 1 the intervention is SeHCAT as the first test in people with symptoms suggestive of functional disease (position B1 in Figure 1).

For population 2 the intervention is SeHCAT.

Comparators

In the economic model the comparator will be no SeHCAT test (the current situation).

Outcomes

The following outcomes will be considered:

- Effect of testing on treatment plan (e.g. surgical or medical management), where information on the appropriateness of the final treatment plan is also reported
- Effect of testing on clinical outcome, (e.g. morbidity and adverse events)
- Prognosis- the ability of test result to predict clinical outcome (e.g. response to treatment)

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).

Study design

The following types of studies will be included:

- Randomised or non-randomised controlled trials, where participants are assigned to the intervention or comparator tests, for treatment planning, and outcomes are compared at follow-up.
- Observational studies which report the results of multi-variable regression modelling with clinical outcome as the dependent variable and index test result as an independent variable. Included studies should control adequately for potential confounders (e.g. age, gender, disease, etc.).

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

5.2. Search strategy

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.[7-9]

Additional supplementary searches will be carried out as necessary. Searches for studies for cost and quality of life will also be included, see Section 6 for further detail.

The following databases will be searched for relevant studies from inception to the present:

- MEDLINE (OvidSP)
- MEDLINE In-Process Citations and Daily Update (OvidSP)
- EMBASE (OvidSP)
- Cochrane Database of Systematic Reviews (CDSR) (Internet)
- Cochrane Central Register of Controlled Trials (CENTRAL) (Internet)
- Database of Abstracts of Reviews of Effects (DARE) (Internet)
- Health Technology Assessment Database (HTA) (Internet)
- Science Citation Index (SCI) (Web of Science)
- NIHR Health Technology Assessment Programme (Internet)

Completed and ongoing trials will be identified by searches of the following resources (up to 2011):

- NIH ClinicalTrials.gov (http://www.clinicaltrials.gov/)
- Current Controlled Trials (http://www.controlled-trials.com/)
- WHO International Clinical Trials Registry Platform (ICTRP) (http://www.who.int/ictrp/en/)
- EU Clinical Trials Register (https://www.clinicaltrialsregister.eu/)

Key conference proceedings, to be identified in consultation with clinical experts, will be screened for the last five years. These may include the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) EUROSON congress.

Identified references will be downloaded in Endnote X4 software for further assessment and handling.

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

Search strategies will be developed specifically for each database and the keywords associated with BAM shall be adapted according to the configuration of each database. The main Embase search strategy for each set of searches was independently peer reviewed by a second Information Specialist, using the PRESS-EBC checklist.[10]

No restrictions on language or publication status will be applied. Limits will be applied to remove animal and phantom 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; these will be adapted as necessary following consultation with clinical experts.

5.3. Data extraction strategy

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.

Data relating to study details, participants, intervention and comparator tests, reference standard, and outcome measures will be extracted by one reviewer, using a piloted, standard data extraction form. A second reviewer will check data extraction and any disagreements will be resolved by consensus or discussion with a third reviewer.

5.4. Quality assessment strategy

The methodological quality of included studies will be assessed using standard tools.[7] The Cochrane Collaboration quality assessment checklist will be used to assess the methodological quality of each included study as detailed in Table 1.[11]

Table 1: The Cochrane Collaboration's Tool for Assessing Risk of Bias[11]

Domain	Item	Description
Sequence Generation	**Was the allocation sequence adequately generated?**	The method used to generate the allocation sequence should be described in sufficient detail to allow an assessment of whether it should produce comparable groups.
Allocation Concealment	**Was allocation adequately concealed?**	The method used to conceal the allocation sequence should be described in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.
Blinding of participants, personnel and outcome assessors *Assessments will be made for each main outcome (or class of outcomes).*	**Was knowledge of the allocated intervention adequately prevented during the study?**	All measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received, should be described. Any information relating to whether the intended blinding was effective should also be reported.
Incomplete outcome data *Assessments will be made for each main outcome (or class of outcomes).*	**Were incomplete outcome data adequately addressed?**	The completeness of outcome data for each main outcome should be described, including attrition and exclusions from the analysis. The authors should report any attrition and exclusions, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions and any re-inclusions in analyses.
Selective outcome reporting	**Are reports of the study free of suggestion of selective outcome reporting?**	The study should be free of the possibility of selective outcome reporting.
Other sources of bias	**Was the study apparently free of other problems that could put it at a high risk of bias?**	Overall, the study should be free from any important concerns about bias (i.e. bias from other sources not previously addressed by the other items).

Each study will be awarded a 'yes', 'no' or 'unclear/unknown' rating for each individual item in the checklist. Any additional clarifications or comments will also be recorded.

The quality of case-control and cohort studies will be assessed using specific checklists for the methodological quality assessment of these studies (see Appendix 2).

Quality assessment will be carried out independently by two reviewers. Any disagreements will be resolved by consensus. 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. In addition, if enough data are available from the included studies, each of the quality components will be included as explanatory variables in a meta-regression analysis to investigate the association of each of these components with study results as a way of explaining possible heterogeneity. Based on the findings of the quality assessment, recommendations will be made for the conduct of future studies.

5.5. Methods of analysis/synthesis

The results of initial scoping searches suggest that trial data and prognostic data are likely to be sparse or non-existent. This section therefore focuses on the synthesis of data from test accuracy studies. If other studies are identified, we anticipate that these will be summarised in a narrative synthesis.

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. Studies will be organised by clinical application (diagnosis of BAM in those with chronic diarrhoea and those with Crohn's disease).

Any data included on the following outcome measures: effects of testing on treatment planning and/or clinical outcome; adverse events associated with testing; acceptability to patients will be summarized according to the size and range of the outcomes reported.

The methods used to synthesis the data will be dependent on the types of outcome data included and the clinical and statistical similarity of the studies. Possible methods include the following types of analysis.

Dichotomous outcomes

Dichotomous data will be analysed by calculating the relative risk (RR) for each trial using the random effects DerSimonian and Laird method and the corresponding 95% confidence intervals (CIs).[12]

Continuous outcomes

Continuous data will be analysed by calculating the standardised mean difference (SMD) between groups and the corresponding 95% CI, due to the different types of outcome measures. If the standard deviations and means are not determinable, they will be estimated from the data that is provided or from a representative value from other studies.

Systematic differences between studies (heterogeneity) are likely; therefore, the random-effects model will be used for the calculation of relative risks or standardised mean differences. Heterogeneity will initially be assessed by measuring the degree of inconsistency in the studies' results (I^2). This measure (I^2) describes the percentage of total variation across studies that were due to heterogeneity rather than the play of chance. The value of I^2 can lie between 0% and 100%. Low, moderate and high I^2 values correspond to 25%, 50%, and 75%.

If important heterogeneity is identified, this will be formally investigated using meta-regression. In particular, a model will be used to explore the possible modifying effects of the following pre-specified factors: methodological quality of the primary studies, underlying illness, duration of pain, different age groups, and gender. The coefficient describing the predictive value of each factor and the overall effect on the main outcome will be modelled, using a fixed-effect model.

A funnel plot (plots of logarithm of the RR for efficacy against the precision of the logarithm of the RR) will be generated in order to estimate potential asymmetry, which will be indicative of small study effects. Treatment discontinuations will be chosen as an outcome since they are likely to be reported by the majority of included studies. In addition, the Egger regression asymmetry test will be used in order to facilitate the prediction of potential publication biases. This test detects funnel plot asymmetry by determining whether the intercept deviates significantly from zero in a regression of the standardised effect estimates against their precision.

Statistical analyses will be performed using the following software: RevMan (version 5), Comprehensive Meta-Analyses (CMA version 2), and STATA (STATA™ for Windows, version 10, Stata Corp; College Station, TX).

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.

6. Report methods for synthesising evidence of cost-effectiveness

6.1 Identifying and reviewing published cost-effectiveness studies

Exploration of the literature regarding published economic evaluations, utility studies and cost studies will be performed in the literature databases listed above. In addition, specific health economic databases will be searched (e.g. NHSEED (NHS Economic Evaluation Database), and HEED (Health Economic Evaluation Database). Searches will focus on original papers that report on cost, cost-accuracy, cost-effectiveness or cost-utility analyses, either studying the diagnostic phase (test accuracy in terms of detecting BAM of patients with chronic diarrhoea), therapeutic phase (patients with BAM), 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. Assessment of methodological quality will follow the criteria for economic evaluations in health care as described in the NICE methodological guidance.[4] 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.

6.2 Evaluation of costs, quality of life and cost-effectiveness

Since this project aims to assess the value of SeHCAT in two different patient populations (see section 4.3 and 4.4), two separate economics models will be defined, constructed, analysed, and reported independently. Both models will evaluate the cost-effectiveness of SeHCAT compared to no SeHCAT as described in section 5.1. The perspective will be that of the NHS and the timeframe used will be life time. Consequences will be expressed as number of correct diagnoses for the diagnostic phase, and (quality adjusted) life years to also include the therapeutic phase. Any assumption used in the models and any parameter value will be based on literature if possible and supplemented by clinical expert opinion as required.

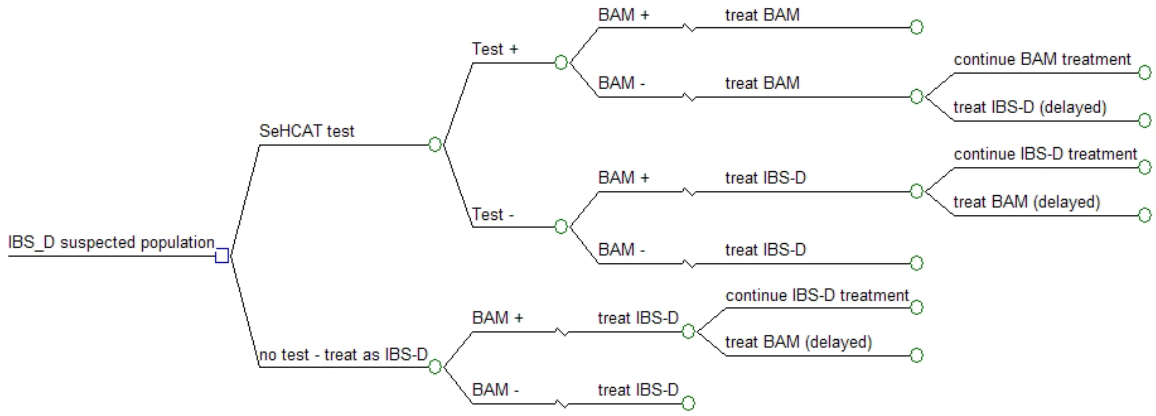
Model structure

Published studies that measure the clinical utility of SeHCAT from initial diagnosis through to final health outcomes have not been identified during the scoping phase. Consequently, it is likely that a linked evidence approach will need to be used in the modelling. That is,

outcomes of the diagnostic tests to be assessed will need to be related to changes in treatment decisions, any delays in diagnosis and final heath outcomes.

An outline of the proposed models is presented in Figure 2 and 3.

Figure 2 Outline of model for patients presenting with chronic diarrhoea with unknown cause and symptoms suggestive of functional disease



The diagnostic part of the model for population 1 is straightforward, including the outcome of SeHCAT (positive or negative) and the true disease status (BAM positive of negative). Both true positives and true negatives are treated according to usual management of BAM and IBS-D. Patients who tested positive for BAM while in fact not having BAM (false positives) are assumed to receive treatment for BAM. The important question that needs to be addressed in this study, most likely using expert opinion, is whether (some of) these patients will be detected at some point as having IBS-D, and how long this delay will last. Likewise, patients who tested negative for BAM while in fact having BAM (false negatives) are assumed to receive treatment for IBS-D. Again, an important question is whether (some of) these patients will be detected at some point as having BAM, and how long this delay will last. Also interesting in this situation is whether some parts of IBS-D management may also be helpful to some extend in patients with BAM, such as changes in diet.

Whether wrongly diagnosed patients will eventually receive a correct diagnosis and the duration of the delay until correct diagnosis is expected to have an important influence on the cost-effectiveness of SeHCAT.

If relevant, this part of the model will also take complications due to the SeHCAT test and the short and long term consequences into account

The therapeutic part of the model requires modelling the life-long costs and effects of treating BAM and IBS-D. For this, a Markov model will be developed. Until now, no modelling studies in IBS and BAM have been identified that may be used in this study. Given the lack of data in this area, we anticipate a simple model structure for the Markov models,

using health states defined based on whether the chronic diarrhoea is resolved or not and possibly including a health state for constipation.

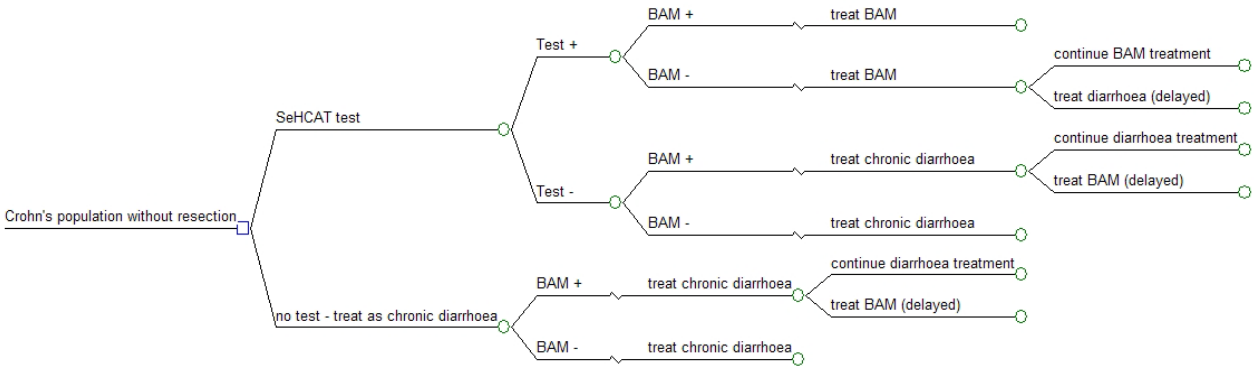
For the treatment of BAM, the treatment of choice is medication with BAS. However, few published trials exist looking at the efficacy of BAS in BAM. It has been suggested that data on efficacy of BAS in other disease areas, such as hyperlipedemia, might be used. However, the endpoints by which the efficacy of BAS is measured will differ between disease areas. Another issue relates to one of the important problems of BAS treatment, i.e. tolerability. It is not unlikely that patients with a high cholesterol level (which does not lead to any symptoms in patients) are less willing to tolerate the side effects of BAS, merely to avoid future cardiovascular problems. For patients with BAM, the relieve from a decrease in bowel movements might well outweigh the side effects. Thus, it is reasonable to expect that little to no data exist to meaningful model the costs and effects of treatment of BAM.
If relevant, the impact of untreated and treated BAM and IBS-D on mortality will be taken into account.

For the treatment of IBS-D, we anticipate that more information is available on the efficacy of (some of) the treatment options. So far, we have performed a search to obtain estimates of costs (of treatments) and utilities in IBS-D, which retrieved 401 references, of which 27 were selected from screening title and abstract. Some of these appear to be useful in terms of being UK based and relatively recent, although full papers are yet to be retrieved. We also intend to perform a similar search for the Crohn's disease population.

For the trial-by-treatment comparator, the model may use data on effectiveness of BAS for those in the model with BAM and assuming that those without BAM have no improvement in symptoms and the same adverse event profiles as those with BAM.

For the second population, we will follow the same model structure. The analysis for this population is about the efficiency of BAS causing symptom relief and avoidance of unnecessary anti-inflammatory treatment (e.g. systemic cortico-steroids).

Figure 3 Outline of model for patients with Crohn's disease and chronic diarrhoea with unknown cause (i.e. before resection of the terminal ileum)



For this model, more information about the diagnostic part of the model needs to be collected (most importantly from experts) in order to establish what the current approach is to chronic diarrhoea in Crohn's patients. And here the same questions arise as in the first population, i.e. whether (some of the) wrongly diagnosed patients are detected and what the delay in detection will be.

The therapeutic part of the model requires modelling the life-long costs and effects of treating BAM or chronic diarrhoea with non-BAM cause through a Markov model. Again, data on efficacy of treatments in this population will be scarce. Although assumptions can be made, and varied in sensitivity analysis and threshold analysis, the question is whether this will lead to any useful conclusions.

Final choices and definitions regarding the structure of the model will depend on the findings from the literature review and consultation with clinical experts. In addition, the existence/availability of any other electronic models that reflect the cost-effectiveness of treatment pathways for these patients, and are representative of current care within the NHS, will be determined.

Issues relevant to analyses:

- Longer term costs and consequences will be discounted using the UK discount rates of 3.5% of both costs and effects.
- One way sensitivity analyses will be performed for all key parameters, especially for parameters in the models which are based on expert opinion.
- Probabilistic sensitivity analyses will be performed using parameter distributions instead of fixed values.
- Decision uncertainty regarding mutually exclusive alternatives will be reflected using cost-effectiveness planes and cost-effectiveness acceptability curves.

Health outcomes
Utility values, based on literature or other sources, will be incorporated in the economic model. When utility values specific for BAM are not available, values for general chronic diarrhoea will be used. QALYs will be calculated from the economic modelling.

Costs
Resource utilisation will be estimated for the diagnostic tests and treatments. 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)), discussions with individual hospitals and with the manufacturers of the comparators.

7. Handling of information from the companies

All data submitted by the manufacturers/sponsors will be considered if received by the EAG no later than 05/03/2012. 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.

8. Competing interests of authors

None

9. Timetable/milestones

Milestones	**Completion data**
Draft protocol	24/11/2011
Final protocol	15/12/2011
Progress report	05/03/2012
Draft assessment report	02/04/2012
Final assessment report	21/05/2012

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Appendix 1

Clinical effectiveness search

Embase search: Facet 1 combined terms for SeHCAT (lines #1-5) and Bile Acid Sequestrants (lines #6-12) using OR in line #13 (n=33829). Facet 2 for Bile Acid Malabsorption (lines #14-20) was then combined with facet 1 using AND in line #21 (n=3044). Line #21 was then combined with both an RCT filter and Non-randomised studies filter and limited to remove animal studies. The final set was then limited to Embase records only in line #33 (n=1172). For the full strategy please see below

Embase (OvidSP): 1980 to 2011 Week 46
Searched: 25.11.11

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1 (tauroselcholic or selenohomocholyltaurine or 75018-71-2).mp. (151)
2 (SeHCAT or Se-HCAT or 75SeHCAT or Se-75 or 75-SeHCAT or SE75).mp. (765)
3 (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).mp. (19)
4 (selenium adj3 "75").mp. (483)
5 or/1-4 (1150)
6 bile acid sequestrant/ (629)
7 ((bile adj3 acid adj3 sequestra$) or BAS).ti,ab,ot,hw,rn. (15990)
8 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. (2486)
9 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. (9021)
10 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 182815-43-6 or 182815-44-7).ti,ab,ot,hw,rn. (693)
11 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 hydroxide 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 brasivil or rocgel or alugel or hydrated alumina or basalgel or dialume or nephrox).ti,ab,ot,hw,rn. (7408)
12 or/6-11 (32747)

13 5 or 12 (33829)
14 (BAM or I-BAM or IBAM or PBAM).mp. (1952)
15 primary bile acid diarrh?ea$.mp. (4)
16 chronic diarrhea/ (2492)
17 ((chronic or watery or recur$ or persist$ or protract$ or continual$ or continuous$ or sustain$ or constant$ or relentless$ or unrelent$ or functional or aggressive) adj2 diarrh?e$).mp. (14493)
18 (malabsorb$ or mal-absorb$ or malabsorp$ or mal-absorp$).mp. (16312)
19 ((bile or biliary) adj3 (acid$ or salt$)).mp. (31246)
20 or/14-19 (61945)
21 13 and 20 (3044)
22 Random$.tw. or placebo$.mp. or double-blind$.tw. (835216)
23 "clinical trial (topic)"/ or "controlled clinical trial (topic)"/ or "multicenter study (topic)"/ or "phase 1 clinical trial (topic)"/ or "phase 2 clinical trial (topic)"/ or "phase 3 clinical trial (topic)"/ or "phase 4 clinical trial (topic)"/ (11859)
24 Clinical article/ or controlled study/ or major clinical study/ or prospective study/ (5272269)
25 (Cohort or compar$ or groups or multivariate).mp. (4685280)
26 or/22-25 (8026182)
27 animal/ (1661955)
28 animal experiment/ (1473625)
29 (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. (4826714)
30 or/27-29 (4826714)
31 exp human/ (12719767)
32 human experiment/ (295041)
33 or/31-32 (12721151)
34 30 not (30 and 33) (3868516)
35 26 not 34 (6217248)
36 21 and 35 (1231)
37 limit 36 to embase (1172)

Based on Trials filter:
Wong SS, Wilczynski NL, Haynes RB. Developing optimal search strategies for detecting clinically sound treatment studies in EMBASE. Journal of the Medical Library Association 2006;94(1):41-7.
&
Based on Non-randomised studies filter: Fixed method B for Embase:
Furlan AD, Irvin E, Bombardier C. Limited search strategies were effective in finding relevant nonrandomized studies. *Journal of Clinical Epidemiology* 2006;59(12):1303-11. [Ovid]

MEDLINE (Ovid SP): 1948 to November Week 3 2011
Searched 25.11.11

1 (tauroselcholic or selenohomocholyltaurine or 75018-71-2).ti,ab,ot,hw,rn. (2)
2 (SeHCAT or Se-HCAT or 75SeHCAT or Se-75 or 75-SeHCAT or SE75).ti,ab,ot,hw,rn. (274)
3 (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).ti,ab,ot,hw,rn. (317)
4 (selenium adj3 "75").ti,ab,ot,hw. (143)
5 or/1-4 (639)
6 ((bile adj3 acid adj3 sequestra$) or BAS).ti,ab,ot,hw,rn. (2567)

7 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. (503)
8 Cholestyramine Resin/ 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 or mk 135 or mk135).ti,ab,ot,hw,rn. (3234)
9 (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 182815-43-6 or 182815-44-7).ti,ab,ot,hw,rn. (155)
10 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 hydroxide 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).ti,ab,ot,hw,rn. (4374)
11 or/6-10 (10353)
12 5 or 11 (10957)
13 (BAM or I-BAM or IBAM or PBAM).ti,ab,ot,hw. (1657)
14 primary bile acid diarrh?ea$.ti,ab,ot,hw. (3)
15 diarrhea/ (35622)
16 ((chronic or watery or recur$ or persist$ or protracted or continual$ or continuous$ or sustain$ or constant$ or relentless$ or unrelent$ or functional or aggressive) adj2 diarrh?e$).ti,ab,ot,hw. (6806)
17 "Bile Acids and Salts"/ (18352)
18 (malabsorb$ or mal-absorb$ or malabsorp$ or mal-absorp$).ti,ab,ot,hw. (13612)
19 ((bile or biliary) adj3 (acid$ or salt$)).ti,ab,ot,hw. (28246)
20 or/13-19 (79804)
21 12 and 20 (1746)
22 randomized controlled trial.pt. (322599)
23 controlled clinical trial.pt. (84057)
24 randomized.ab. (227373)
25 placebo.ab. (130354)
26 randomly.ab. (163568)
27 trial.ab. (235465)
28 groups.ab. (1082545)
29 or/22-28 (1586402)
30 Clinical Trials as Topic/ or Clinical Trials, Phase I as Topic/ or Clinical Trials, Phase II as Topic/ or Clinical Trials, Phase III as Topic/ or Clinical Trials, Phase IV as Topic/ or Controlled Clinical Trials as Topic/ (173991)
31 Cohort studies/ or comparative study/ or follow-up studies/ or prospective studies/ (2204429)
32 (Cohort or compar$ or groups or multivariate).ti,ab,ot,hw. (4454648)
33 or/30-32 (4921469)
34 29 or 33 (5121407)
35 animals/ not (animals/ and humans/) (3630436)

36 34 not 35 (4030238)
37 21 and 36 (532)

Based on Trials filter:
Lefebvre C, Manheimer E, Glanville J. Chapter 6: searching for studies. Box 6.4.c: Cochrane Highly sensitive search strategy for identifying randomized controlled trials in Medline: Sensitivity-maximizing version (2008 version); OVID format. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.1 [updated September 2008]. The Cochrane Collaboration, 2008. Available from www.cochrane-handbook.org
&
Based on Non-randomised studies filter: Fixed method B:
Furlan AD, Irvin E, Bombardier C. Limited search strategies were effective in finding relevant nonrandomized studies. *Journal of Clinical Epidemiology* 2006;59(12):1303-11. [Ovid]

Appendix 2

Checklists for the methodological quality assessment of case-control and cohort studies:

A. Case-control studies

- Is the case definition explicit?
- Has the disease state of the cases been reliably assessed and validated?
- Were the controls randomly selected from the source of population of the cases?
- Were interventions and other exposures assessed in the same way for cases and controls?
- How was the response rate defined?
- Were the non-response rates and reasons for non-response the same in both groups?
- Is it possible that over-matching has occurred in that cases and controls were matched on factors related to exposure?
- Was an appropriate statistical analysis used (matched or unmatched)?

B. Cohort studies

- Is there sufficient description of the groups and the distribution of prognostic factors?
- Are the groups assembled at a similar point in their disease progression?
- Is the intervention/treatment reliably ascertained?
- Were the groups comparable on all important confounding factors?
- Was there adequate adjustment for the effects of these confounding variables?
- Was a dose-response relationship between intervention and outcome demonstrated?
- Was outcome assessment blind to exposure status?
- Was follow-up long enough for the outcomes to occur?
- What proportion of the cohort was followed-up?
- Were drop-out rates and reasons for drop-out similar across intervention and unexposed groups?

Appendix 3
NICE guidelines on interventions for the treatment of chronic diarrhoea:

None.

Other relevant guidelines:

- Irritable bowel syndrome in adults: Diagnosis and management of irritable bowel syndrome in primary care. February 2008. Available from http://guidance.nice.org.uk/CG61

- Mowat *et al* (2011) Guidelines for the management of inflammatory bowel disease in adults. Gut; 60:571-607.